I. VİRAL İNFEKSİYONLAR VE BAĞIŞIKLAMA SİMPOZYUMU

KLİMİK

HIV ve Direnç

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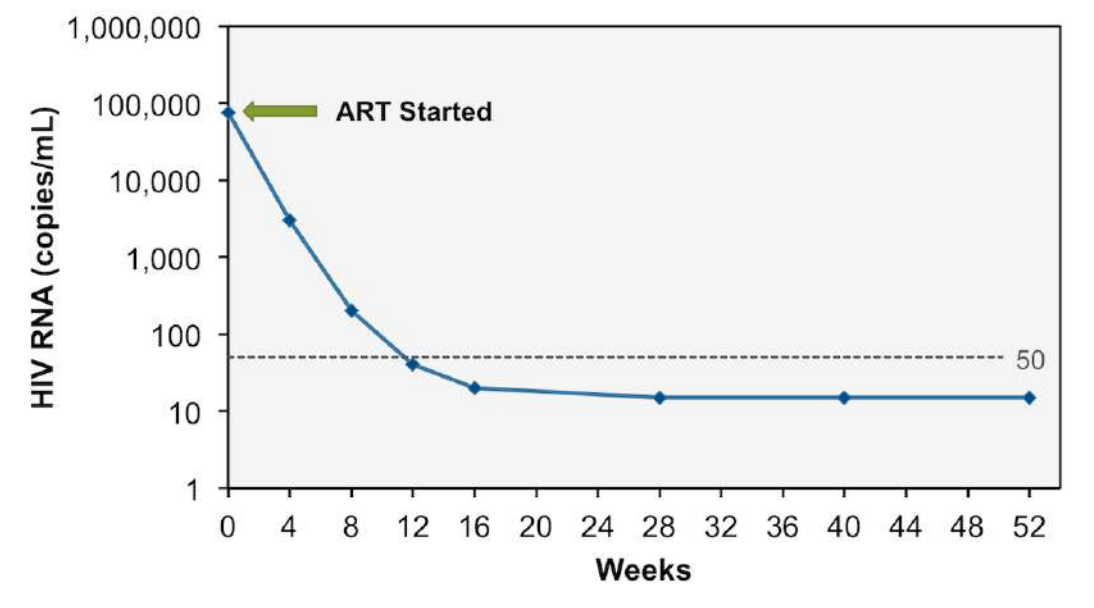
Marmara Üniversitesi Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

MARMARA ÜNİVERSİTESİ 1883 Tıp Fakültesi

21 EYLÜL 2024

Virolojik baskılama (supression)



- Antiretroviral tedavinin (ART) ana hedefi virolojik baskılamayı sağlamak
  - Hedef: ART'nin 6. ayında <50 kopya/mL
  - ART'nin en az 2 tercihen 3 **tam aktif ilaç** ile yapılması önerilir
- HIV tanısı konduğunda direnç testi istenmeli
  - aktarılmış ilaç direncini belirlemek
- Antiretroviral tedavi (ART) tanı sonrası hemen başlamadı ise ART başlamadan önce tekrar istenmeli (tedavi öncesi direnç testi)
- Genotipik direnç testi ART başlanmasını geciktirmemeli
  - sonuç geldiğinde ART tekrar düzenlenebilir
  - direnç sonucu görmeden tedavi başlanacak ise ilk seçenek ilaçlardan yüksek genetik bariyerli olanlar seçilmeli

DHHS 2.2024
EACS v12 10.2023
HIV/AIDS tanı, izlem ve tedavi el kitabı v3 2.2024

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV

What to Start: Initial Combination Antiretroviral Regimens for People With HIV

Updated: September 12, 2024
Reviewed: September 12, 2024

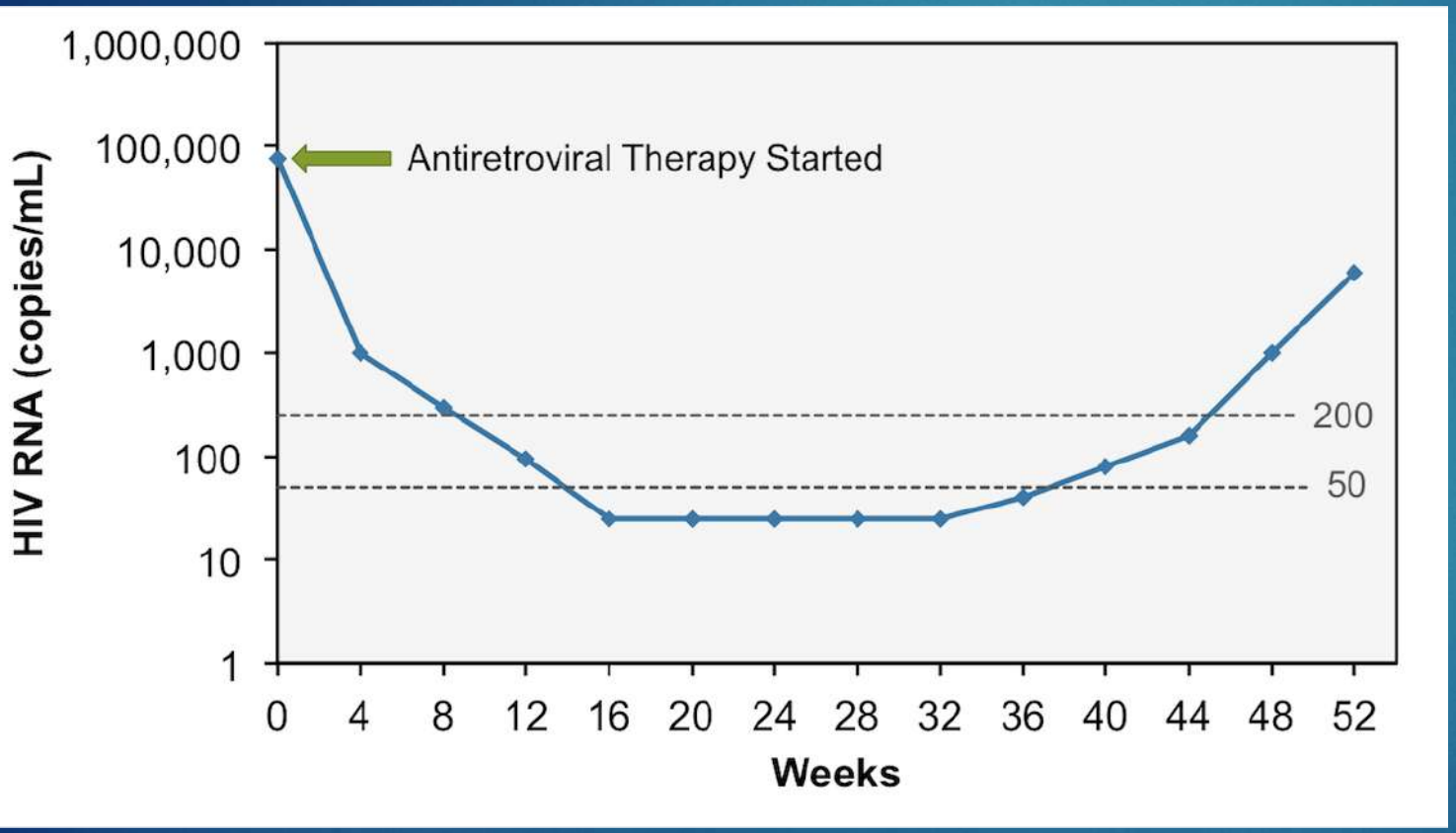
For people who do not have a history of using CAB-LA as PrEP, one of the following regimens is recommended[a]:

- BIC/TAF/FTC **(AI)**
- DTG plus (TAF or TDF)[b] plus (FTC or 3TC) **(AI)**
- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

For people who have a history of CAB-LA use as PrEP, INSTI genotype resistance testing should be performed before starting ART. If ART is to be started before results of genotypic testing results, the following regimen is recommended:

- DRV/c[c] or DRV/r with (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

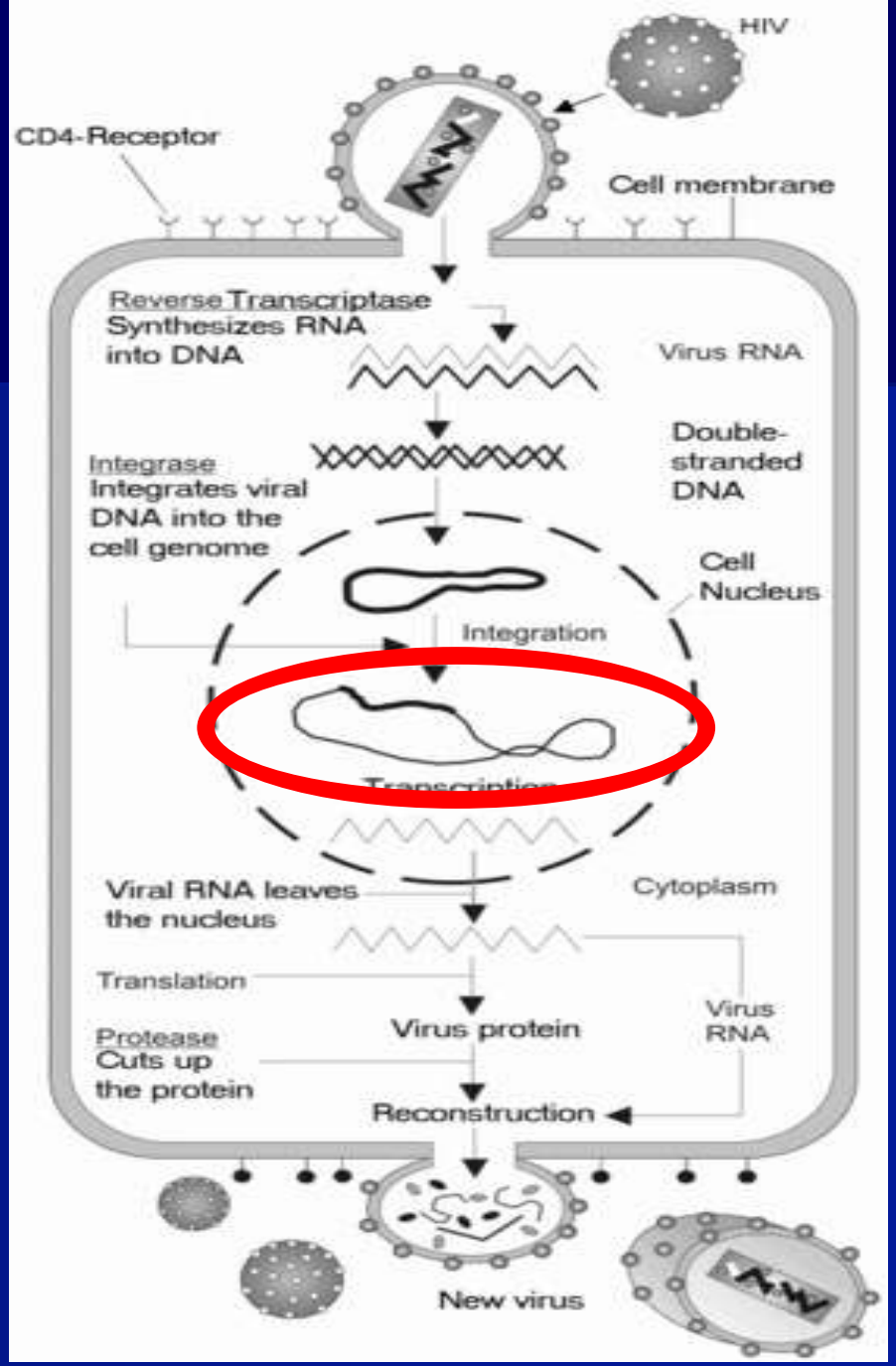
Virolojik kaçış (rebound)



- Virolojik başarısızlıkta ART değişimi öncesi direnç testi istenmelidir
- Viral yük tercihen >500 – 1000 kopya/mL olmalıdır

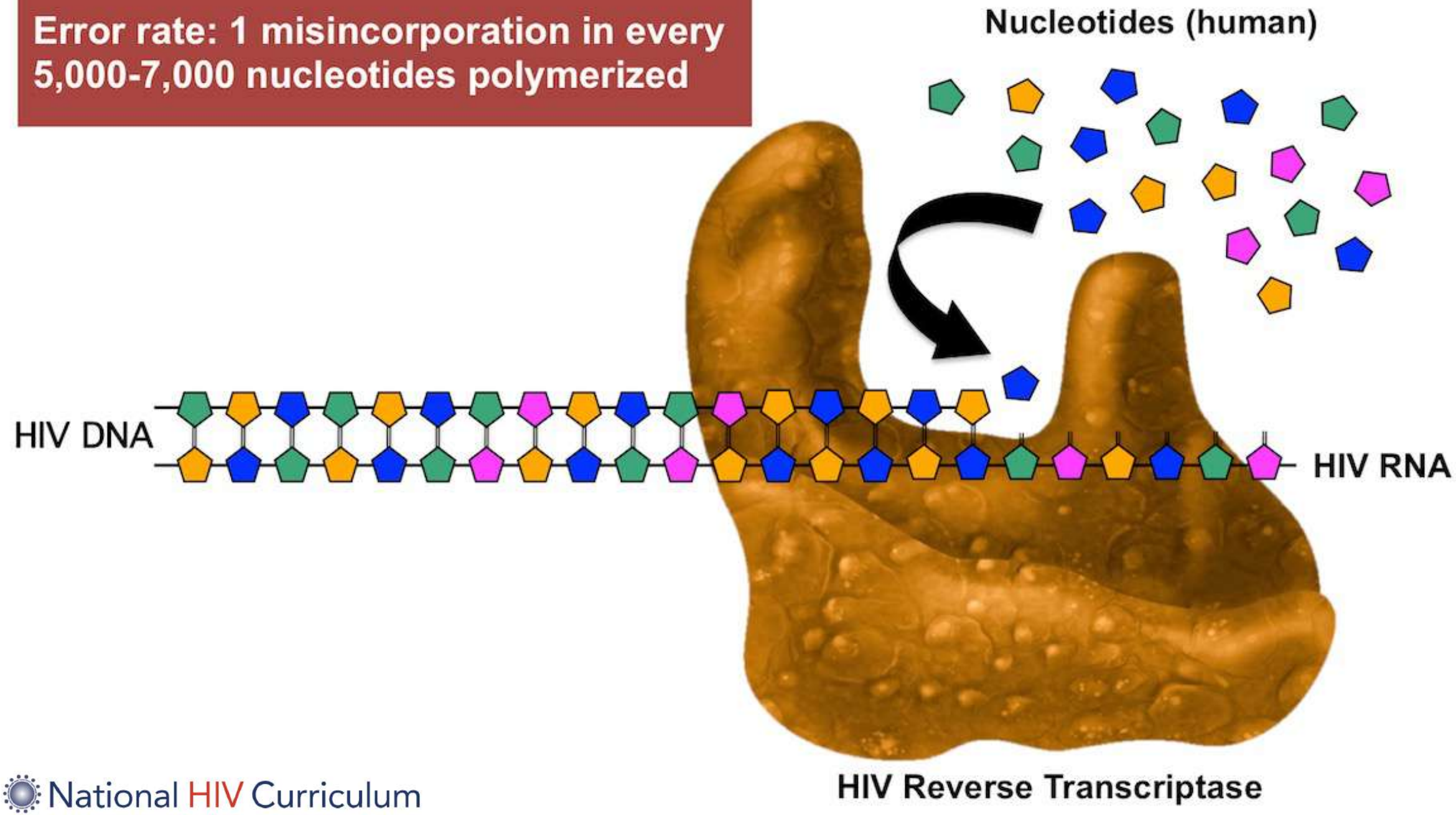
HIV replikasyonu

- Yüksek genetik çeşitlilik
- Hızlı replikasyon döngüsü
  - 10^{9}-10^{10} virion/gün
- Yüksek mutasyon hızı
  - 10^{-3}-10^{-4}/ nükleotid
  - DNA virüslerinde: 10^{-8}-10^{-11}/ nükleotid
  - RT'nin rekombinasyon potansiyeli
  - 1-10 mutasyon/genom

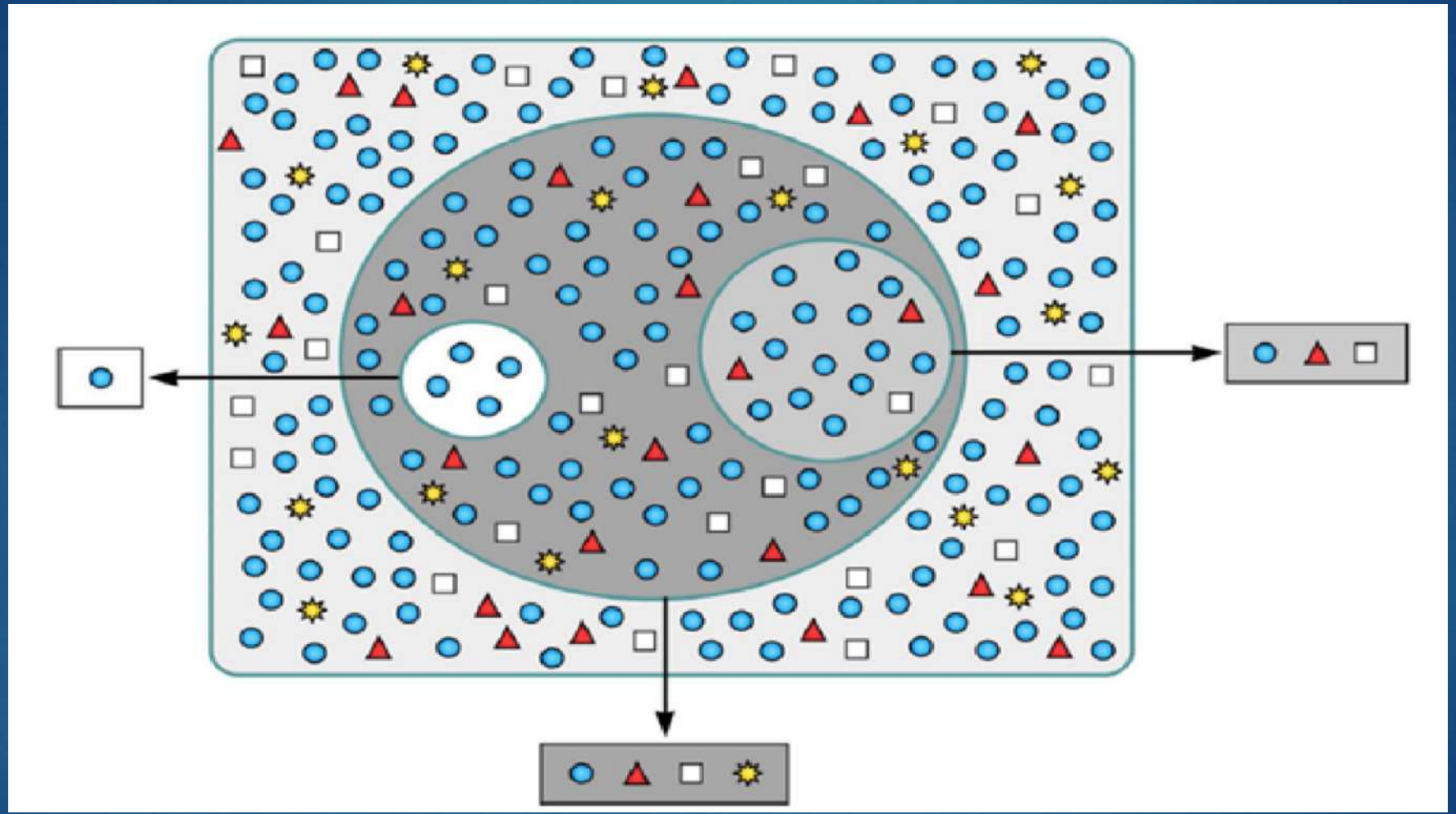


Principles of Molecular Virology, 3rd ed.

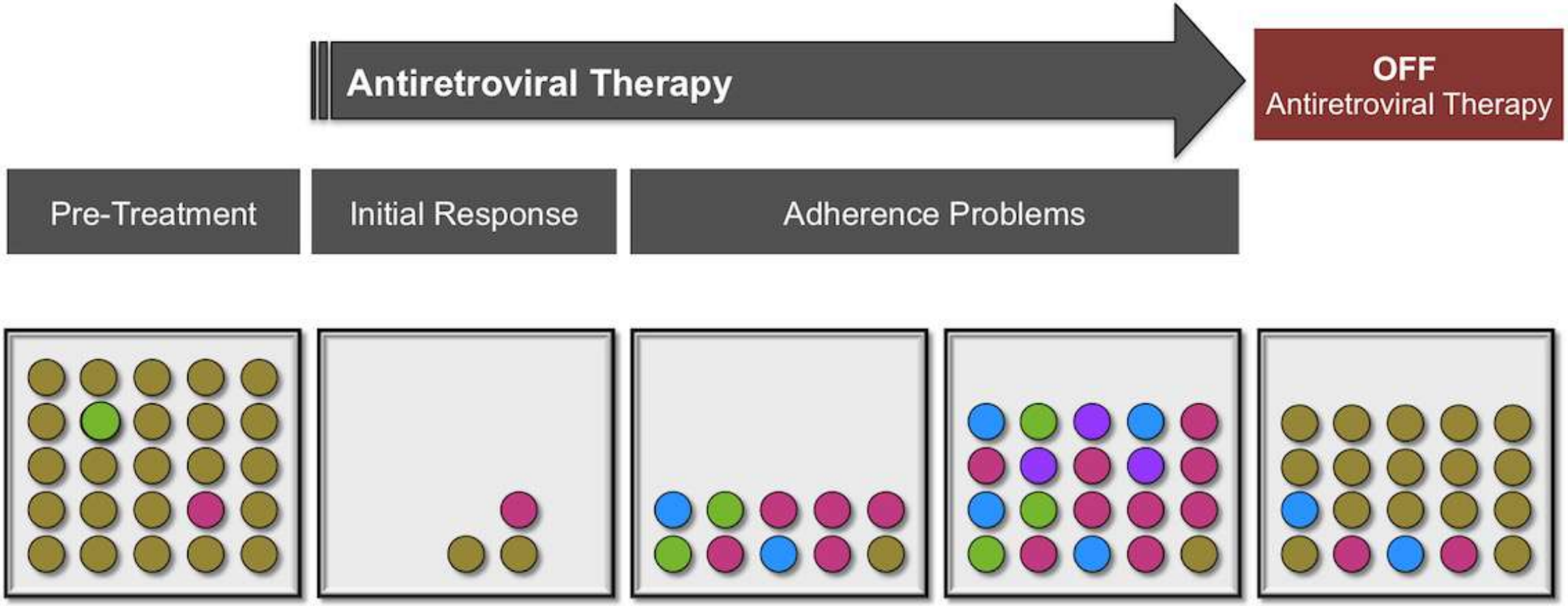
Error rate: 1 misincorporation in every 5,000-7,000 nucleotides polymerized

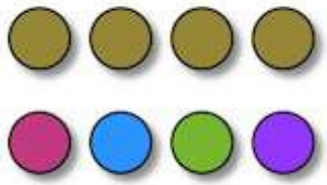


Quasispecies (Türümsü)



https://journals.asm.org/doi/10.1128/MMBR.05023-11
https://doi.org/10.1128/MMBR.05023-11





Wild Type HIV

Resistant HIV

- Direnç testi, hasta başarısız **ART rejimini alırken** yapılmalıdır
- Eğer başarısız ART kesildi ise direnç testi ilaç kesildikten sonraki **4 hafta içerisinde** yapılmalıdır
- ART kesileli 4 haftayı geçti ise hala direnç testi yapılabilir ama ilaç baskısı kaybolduğundan ilaç ile ilişkili mutasyonlar saptanmayabilir

Basic Principles and Clinical Relevance of the IAS–USA 2022 Update of the Drug Resistance Mutations in HIV-1 (On-Demand)

Factors influencing long-term viral suppression

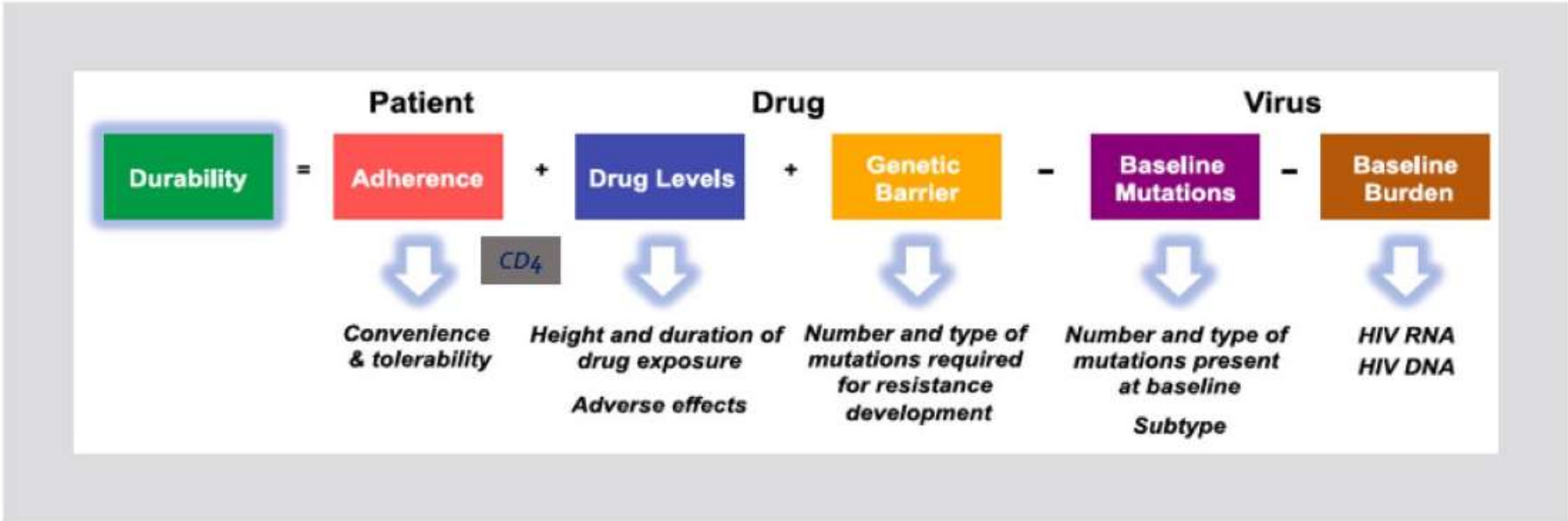
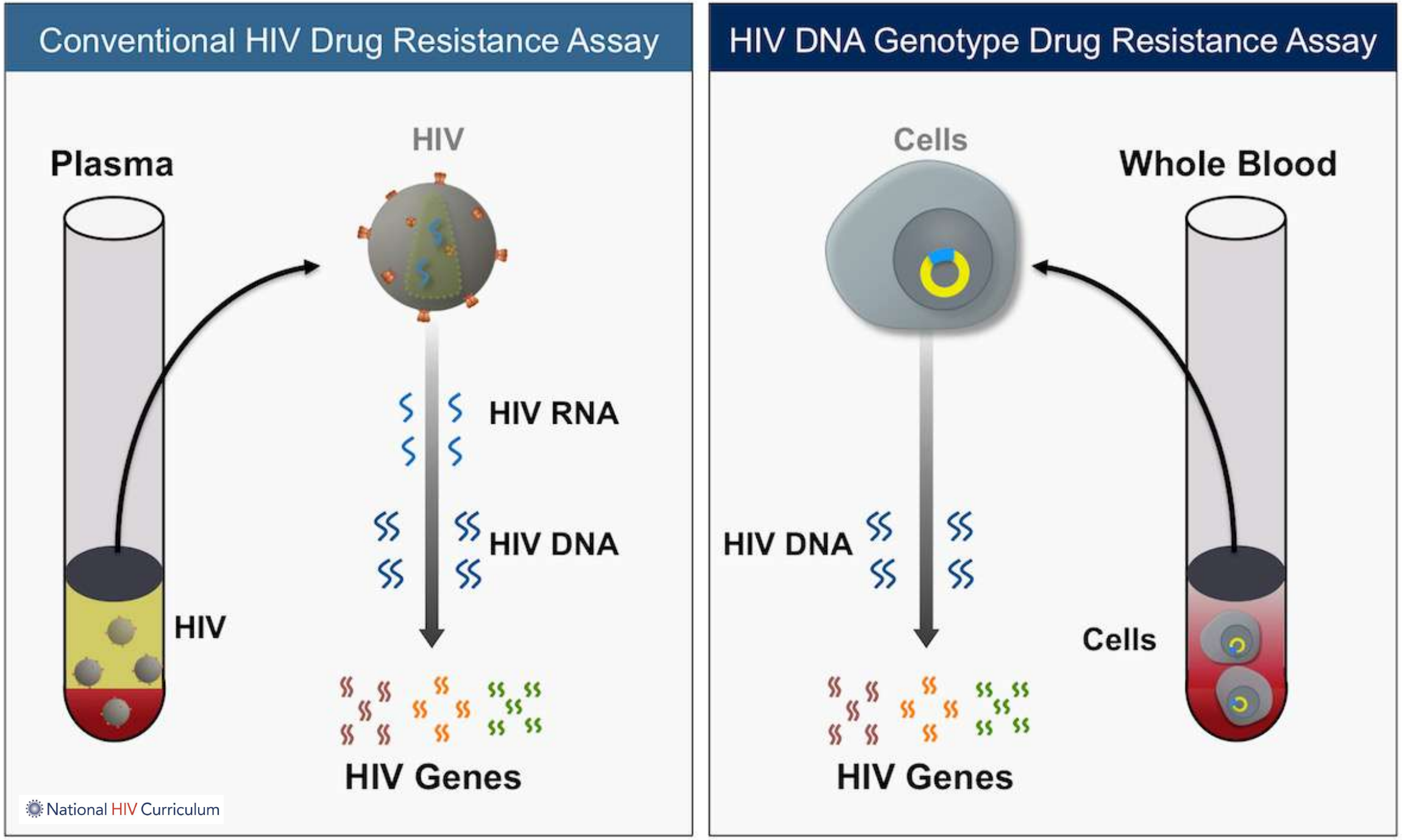


Figure 1. *Factors influencing long-term viral suppression, adapted from Massimo Andreoni personal communicaton.*

Due to the intrinsic characteristics of HIV, the knowledge of several viral parameters at the HIV diagnosis is crucial for the success of all regimens

Svicher et al , Impact Study Group. AIDS Reviews 2017


Conventional HIV Drug Resistance Assay
Plasma
HIV
HIV RNA
HIV DNA
HIV
HIV Genes
National HIV Curriculum
HIV DNA Genotype Drug Resistance Assay
Cells
Whole Blood
HIV DNA
Cells
HIV Genes

HIV ve Antiretroviral İlaçlara Direnç

Direnç Testleri

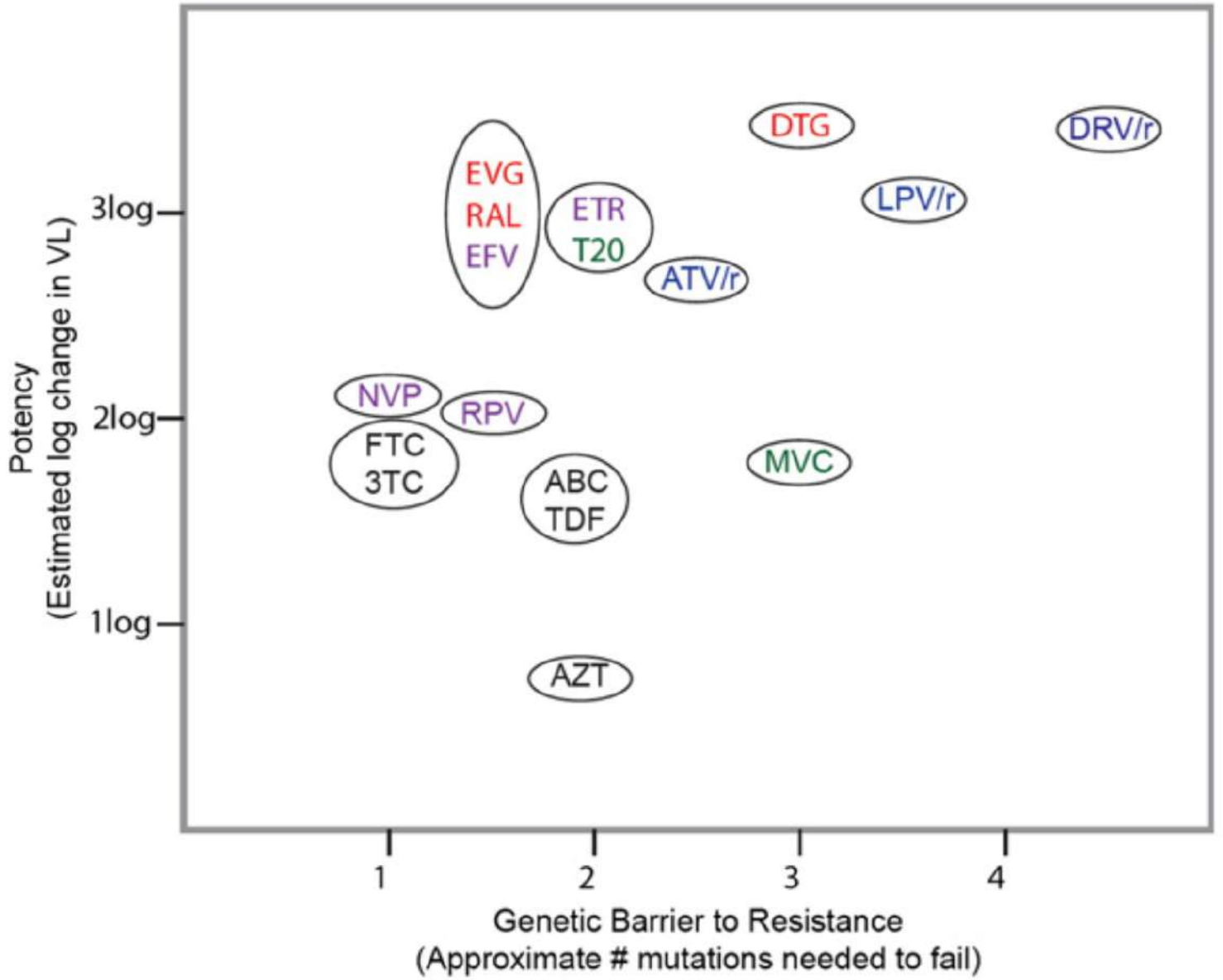
Doç. Dr. Uluhan Sili

GSK HIV KAMPÜS

Güçlü yarınlar için güçlü eğitimler.

NP-TR-HVU-VID-220002

Antiretroviral İlaçların Gücü (potency) ve Genetik Bariyeri



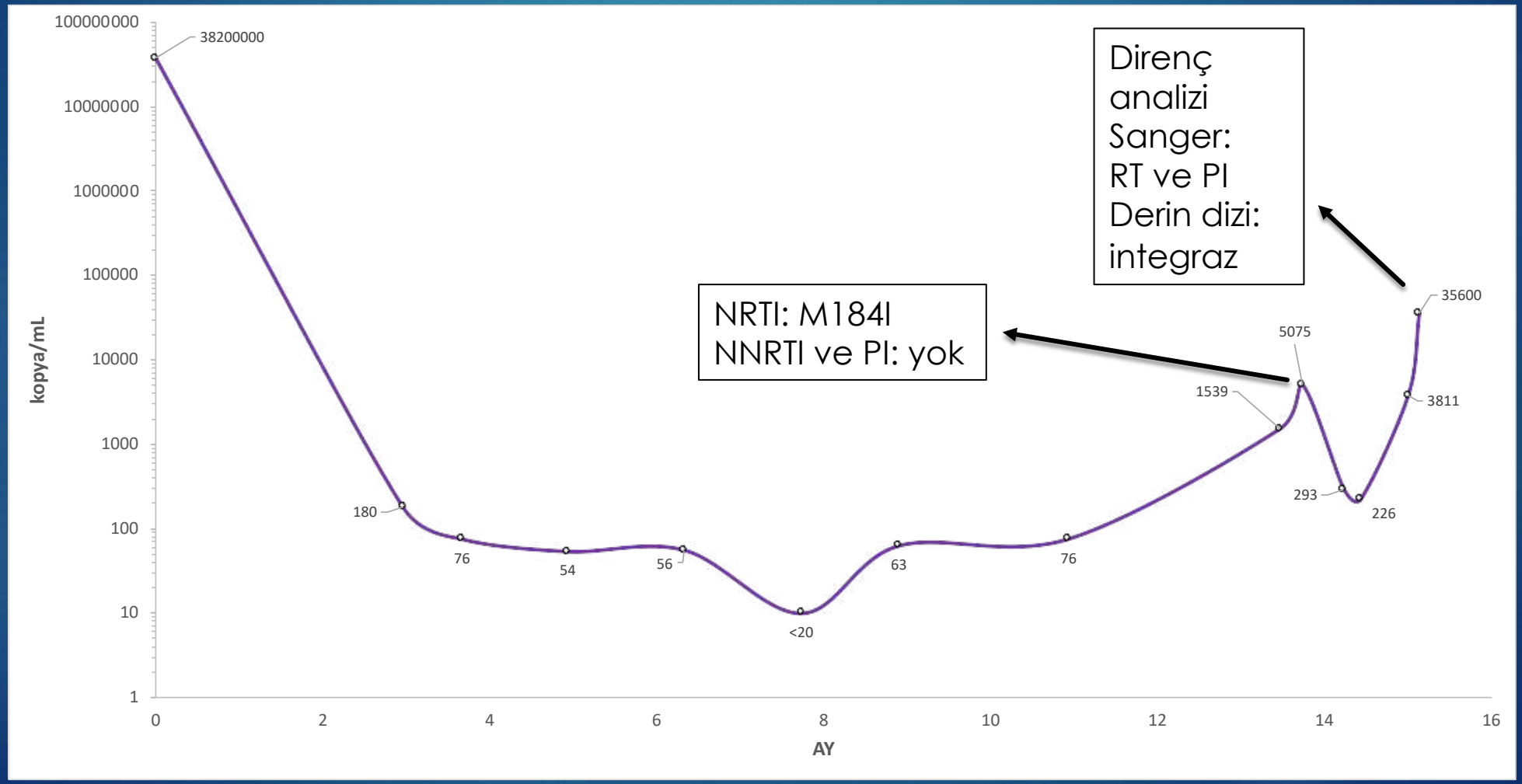
HIV-1 drug resistance and resistance testing

Dana S. Clutter, MD [a,*], Michael R. Jordan, MD, MPH [b,c], Silvia Bertagnolio, MD [d], Robert W. Shafer, MD [a]

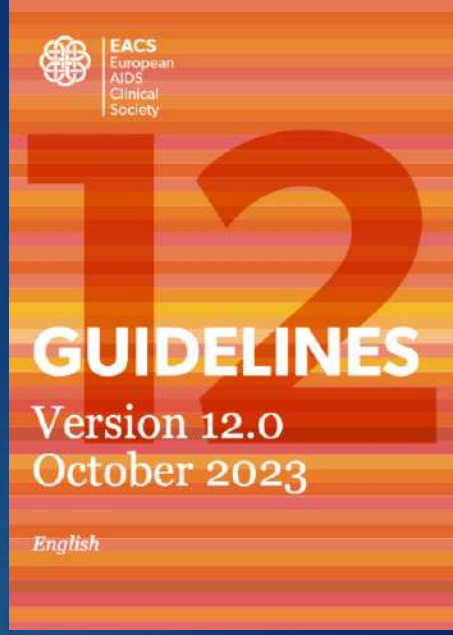
Infection, Genetics and Evolution 46 (2016) 292–307

Olgu (raltegravir)

TDF/FTC + LPV/r | TDF/FTC + RAL (2x400 mg) + HREZ | TDF/FTC + RAL

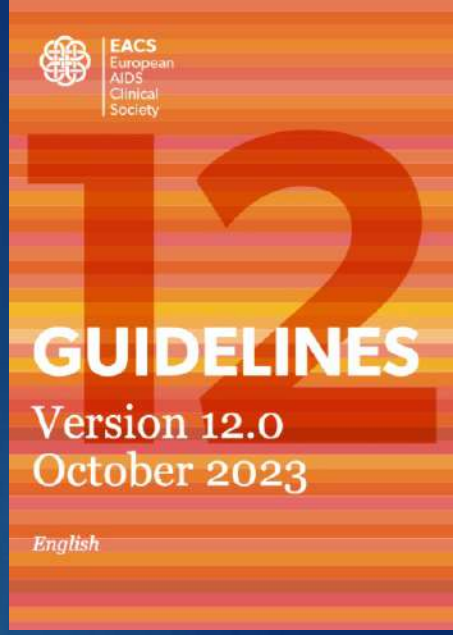


Virolojik Başarısızlık
Genel Yaklaşım



- Mevcut rejimin gücü?
  - önceki direnç testi sonuçları (genotiplemeler)?
  - ART geçmişini inceleyin
- Uyum/ tolere edilebilirlik/ ilaç-ilaç etkileşimleri/ ilaç-gıda etkileşimleri/ psikososyal sorunlarını değerlendirin
- Direnç testi yapın, arşiv mutasyonları
- Maraviroc (CCR5 reseptör antagonisti) düşünülüyorsa tropizm testi
- İlaç düzeyi belirlenmesini (TDM, therapeutic drug monitoring) düşünün
- Tedavi seçeneklerini, aktif ve potansiyel olarak aktif ilaçları/ kombinasyonları belirleyin

Virolojik Başarısızlık *Yönetim*

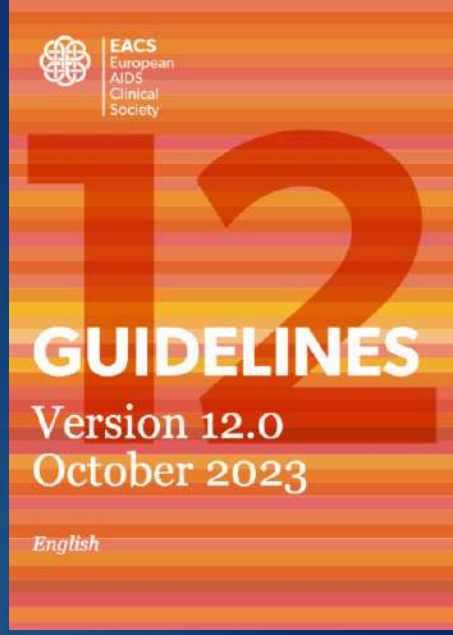


Doğrulanmış viral yük >200 kopya/mL ise:

Terapötik karar, direnç testi (genotipleme) sonuçlarına göre belirlenir:

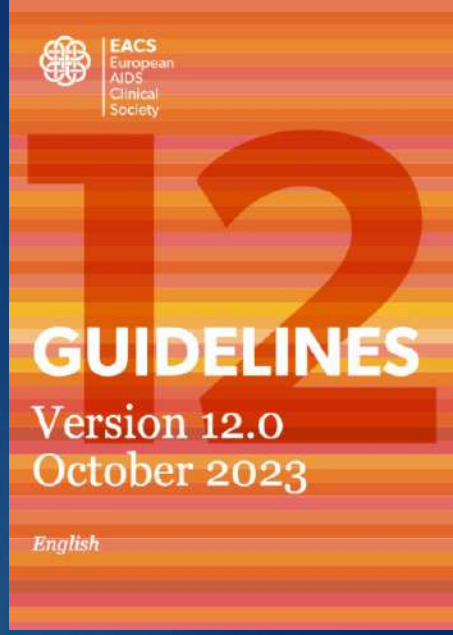
- Direnç mutasyonu bulunmazsa:
  - uyumu kontrol edin, uyumu güçlendirin, TDM uygulayın, farklı bir rejime değişikliği tartışın
  - *hücresel proliferasyon nedeniyle baskılanamayan viremi düşünün (daha çok >50 - <200 k/mL için geçerli)*
  - *ilaç baskısı olmadığında bazı mutasyonların geri dönebileceğini ve/veya ortadan kalkabileceğini göz önünde bulundurun (direnç testi ilaç alırken veya bırakmışsa 4 hafta içerisinde çalışılmalı)*
- Direnç mutasyonları bulunursa:
  - ilaç ve genotipleme geçmişine dayalı baskılayıcı rejime geçin
  - çok sınıflı direnç durumunda tavsiye edilen çok disiplinli uzman tartışması
- Yeni rejimin hedefi: 6 ay içinde HIV-VL < 50 kopya/mL

Virolojik Başarısızlık
Direnç saptandığında yapılacaklar



- En az 2 tercihen 3 tam aktif ilaç kullanın
  - güncel ve önceki direnç analizlerine dayalı olarak
- Sınırlı NRTI mutasyonu saptandı: M184V ve/veya 1-2 TAM
  - 2 NRTI (3TC veya FTC artı TDF veya TAF)
    ve 1 aktif PI/b (ör: DRV/b) veya BIC veya DTG (RAL veya NNRTI önerilmez)
- Çok sınıflı (≥ 2 sınıf) saptandı:
  - en az 1 tam aktif PI/b (ör: DRV/b)
    veya 1 tam aktif 2. nesil INSTI (BIC, DTG)
  - artı sınıftaki diğer ilaçlara karşı dirence rağmen tam olarak aktif kalan 1 veya 2 ilaç (yani 1 veya 2 NRTI ve/veya DOR)
  - ve/veya daha önce kullanılmayan bir sınıftan, ör: INSTI, NNRTI, PI/b, genotipik testle değerlendirilmiş

Virolojik Başarısızlık
Direnç saptandığında yapılacaklar



- NRTI, NNRTI, PI/b ve INSTI ile 2-3 ilaçlı aktif rejim oluşturulamadığında
  - yeni etki mekanizmalı fostemsavir, lenacapavir veya ibalizumab eklenebilir
- Hiç bir durumda monoterapi önerilmemektedir
- < 2 aktif ilaç mevcutsa ART değişikliğinin geciktirilmesine olgu bazlı karar verin
  - düşük CD4 sayısı (< 100 hücre/µL) olan veya eski ilaçları da kullanarak HIV-VL'nin kısmen azaltılması (> 1 $\log_{10}$ kopya/mL azalma) yoluyla bağışıklık fonksiyonunun korunması hedef olan yüksek klinik bozulma riski olan hastalar
- Diğer hususlar:
  - tedaviye ara verilmesi önerilmez
  - belgelenmiş direnç mutasyonu (M184V/I) olsa bile 3TC veya FTC'nin devamı faydalı olabilir
- Birçok seçenek mevcutsa, tercih edilen seçim kriterleri şunları içerir:
  - rejimin basitliği, toksisite risklerinin değerlendirilmesi, ilaç-ilaç etkileşimleri ve gelecekteki kurtarma tedavisinin korunması

Viral *fitness*

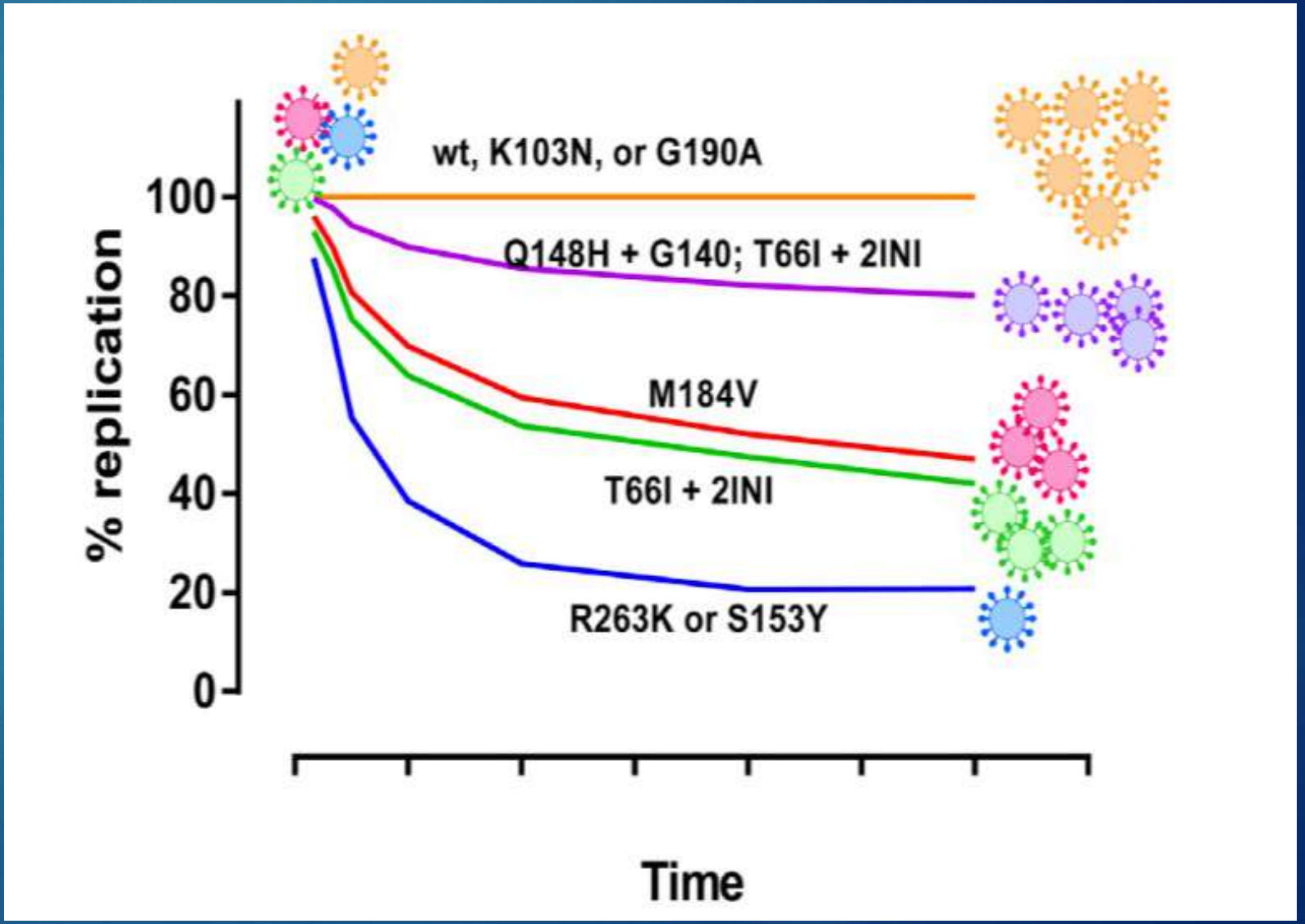
(fitness: belirli bir ortamda üremeye elverişlilik)

Clinical benefit of dolutegravir in HIV-1 management related to the high genetic barrier to drug resistance

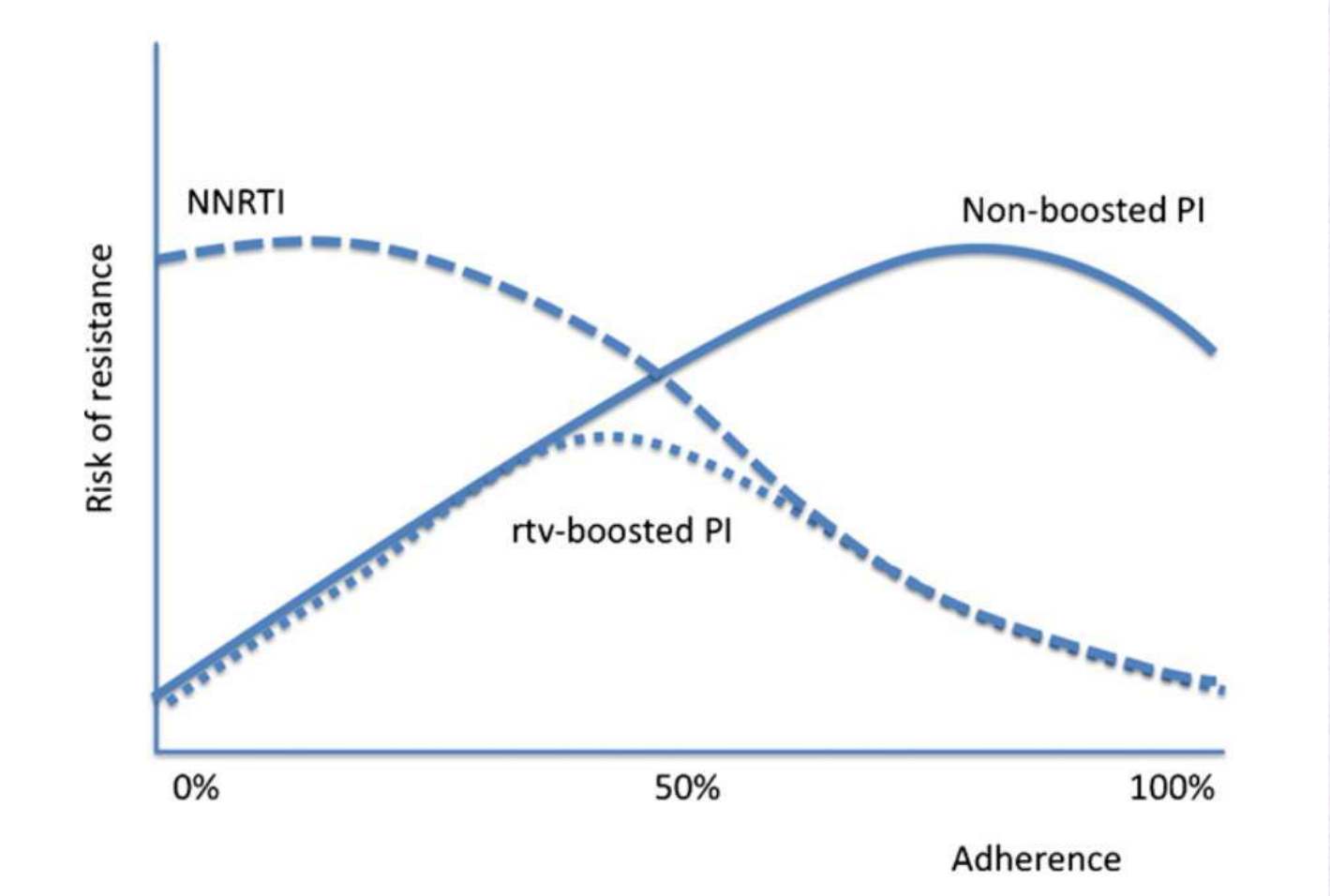
Bluma G. Brenner, Mark A. Wainberg*

Virus Res. (2016)

McGill University AIDS Centre, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada



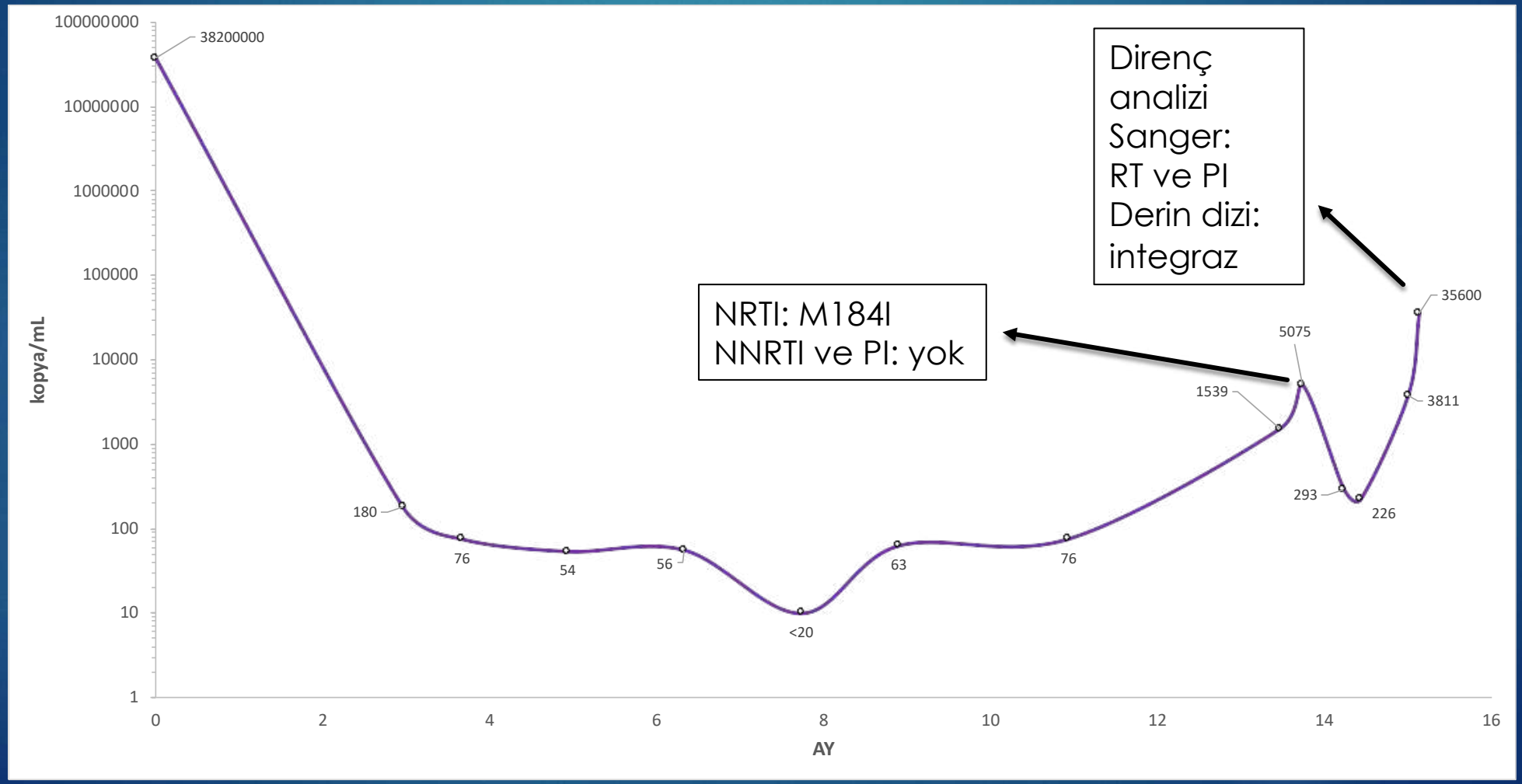
Tedavi Uyumu ve İlaç Direnç Gelişimi Arasındaki İlişki



R. Paredes, B. Clotet / Antiviral Research 85 (2010) 245–265

Olgu (raltegravir)

TDF/FTC + LPV/r | TDF/FTC + RAL (2x400 mg) + HREZ | TDF/FTC + RAL | TDF/FTC + DRV + r



2019 Update of the Drug Resistance Mutations in HIV-1

TDF/FTC + RAL

IAS–USA drug resistance mutations list

	K65R/E/N	L74V	Y115F	M184V/I	L210W / T215Y/F / K219Q/E
Abacavir[1,6]	65 R E N	74 V	115 F	184 V	
Emtricitabine	65 R E N			184 V I	
Lamivudine	65 R E N			184 V I	
Tenofovir[1,7]	65 R E N				

	M41L	D67N	K70R	L210W / T215Y/F / K219Q/E
Zidovudine[4,5,8,9]	41 L	67 N	70 R	210 W / 215 Y F / 219 Q E

NRTI: M184I

Stanford University- HIV Drug Resistance Database
Genotypic Sensitivity Score (GSS)

Toplam Puan	Direnç Yorumu	Klinik Anlamı	GSS
0 - 9	**Duyarlı (susceptible)**	**Yabanıl tiple karşılaştırıldığında ilaç duyarlılığı aynı**	**1**
10 - 14	Olası düşük düzey direnç (potential low-level resistance)	Büyük olasılıkla duyarlı ancak önceden ilaç maruziyeti var	**0.75**
15 - 29	Düşük düzey direnç (low-level resistance)	Azalmış in vitro ilaç duyarlılığı ve/veya olası suboptimal virolojik yanıt	**0.50**
30 - 59	Orta düzey direnç (intermediate resistance)	Sadece yüksek genetik bariyerliyse (PI/r) veya az seçenek varsa bu ilacı kullan	**0.25**
≥60	**Yüksek düzey direnç (high-level resistance)**	**En yüksek in vitro direnç ve/veya bu ilaca hastalarda virolojik yanıt yok**	**0**

Drug resistance interpretation: RT — HIVDB 9.0 (2021-02-22)

NRTI Resistance Mutations:	**M184I**
NNRTI Resistance Mutations:	None
Other Mutations:	None

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Susceptible
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

TDF/FTC + RAL

RT comments

NRTI

- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication.

Mutation scoring: RT — HIVDB 9.0 (2021-02-22)

NRTI	ABC	AZT	FTC	3TC	TDF
M184I	15	-10	60	60	-10
Total	15	-10	60	60	-10

NNRTI	DOR	EFV	ETR	NVP	RPV
Total	0	0	0	0	0

2019 Update of the Drug Resistance Mutations in HIV-1

TDF/FTC + RAL

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS[25]

Drug	51	66	74	92	97	118	121	138	140	143	147	148	153	155	157	263
Bictegravir[26]						G118R		E138K	G140S			Q148H				R263K
Cabotegravir[27]		T66K				G118R		E138A/K/T	G140A/C/R/S			Q148H/K/R	S153F/Y	N155H		R263K
Dolutegravir[28]						G118R	F121Y	E138A/K/T	G140A/S			Q148H/K/R		N155H		R263K
Elvitegravir[29]	H51Y	T66I/A/K		E92Q/G	T97A		F121Y				S147G	Q148H/K/R		N155H	E157Q	R263K
Raltegravir[30]			L74M	E92Q	T97A		F121Y	E138A/K	G140A/S	Y143R/H/C		Q148H/K/R		N155H		R263K

INSTI: Q148R (%99.5), E138K (%92.8)

Drug resistance interpretation: IN — HIVDB 9.0 (2021-02-22)

IN Major Resistance Mutations:	**E138K, Q148R**
IN Accessory Resistance Mutations:	None
Other Mutations:	None

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Intermediate Resistance
cabotegravir (CAB)	High-Level Resistance
dolutegravir (DTG)	Intermediate Resistance
elvitegravir (EVG)	High-Level Resistance
raltegravir (RAL)	High-Level Resistance

TDF/FTC + RAL

IN comments

IN Major

- **E138K/A** are non-polymorphic mutations selected in patients receiving RAL, EVG, and DTG. They usually occur in combination with Q148 mutations. Alone they do not reduce INSTI susceptibility. However, when they occur in combination with Q148 mutations, they are associated with high-level resistance to RAL and EVG and intermediate reductions in DTG and BIC susceptibility. E138T is an uncommon nonpolymorphic INSTI-selected mutation that appears to have an effect similar to **E138K/A**.
- **Q148H/K/R** are non-polymorphic mutations selected by RAL, EVG, and rarely DTG. They nearly always occur in combination with G140A/S or E138K. In this setting they are associated with near complete resistance to RAL and EVG, high-levels of reduction in CAB susceptibility, and intermediate reductions in DTG and BIC susceptibility. The presence of **Q148H/K/R** plus two INSTI DRMs is usually associated with high-level reductions in susceptibility to all INSTIs.

Dosage Considerations

- There is evidence for intermediate **DTG** resistance. If **DTG** is used, it should be administered twice daily.

Mutation scoring: IN — HIVDB 9.0 (2021-02-22)

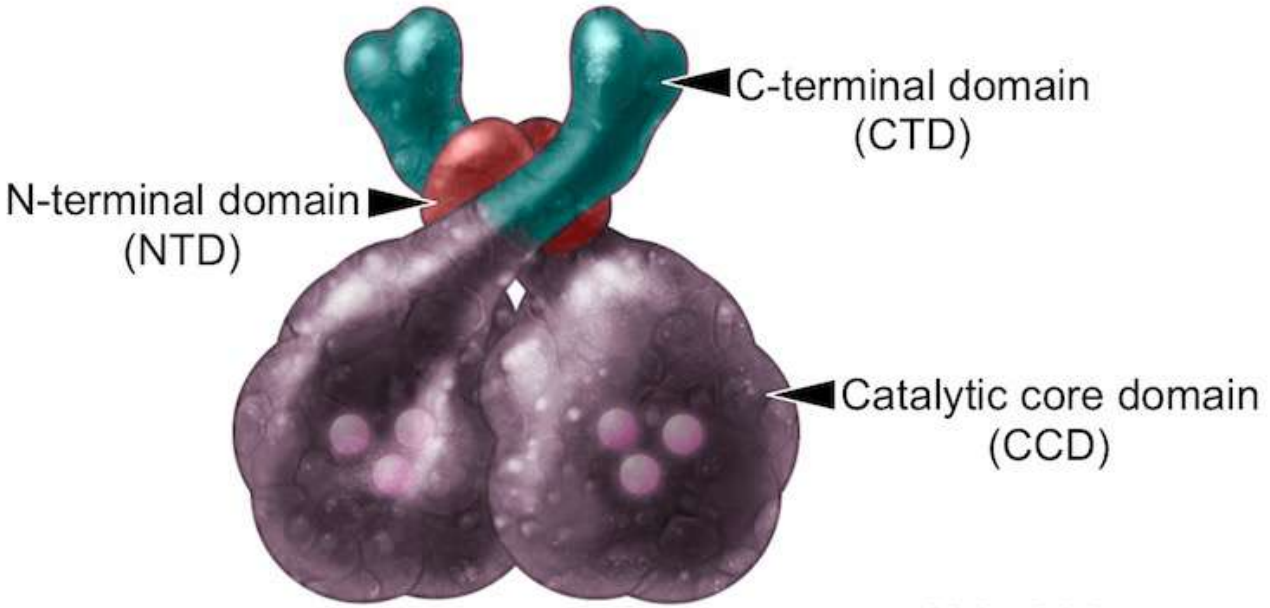
INSTI	BIC	CAB	DTG	EVG	RAL
E138K	10	10	10	15	15
E138K + Q148R	10	20	10	0	0
Q148R	25	40	25	60	60
Total	45	70	45	75	75

Dolutegravir kullanılırsa 2x50 mg po olarak kullanılmalı!

Major Primary Integrase Mutations

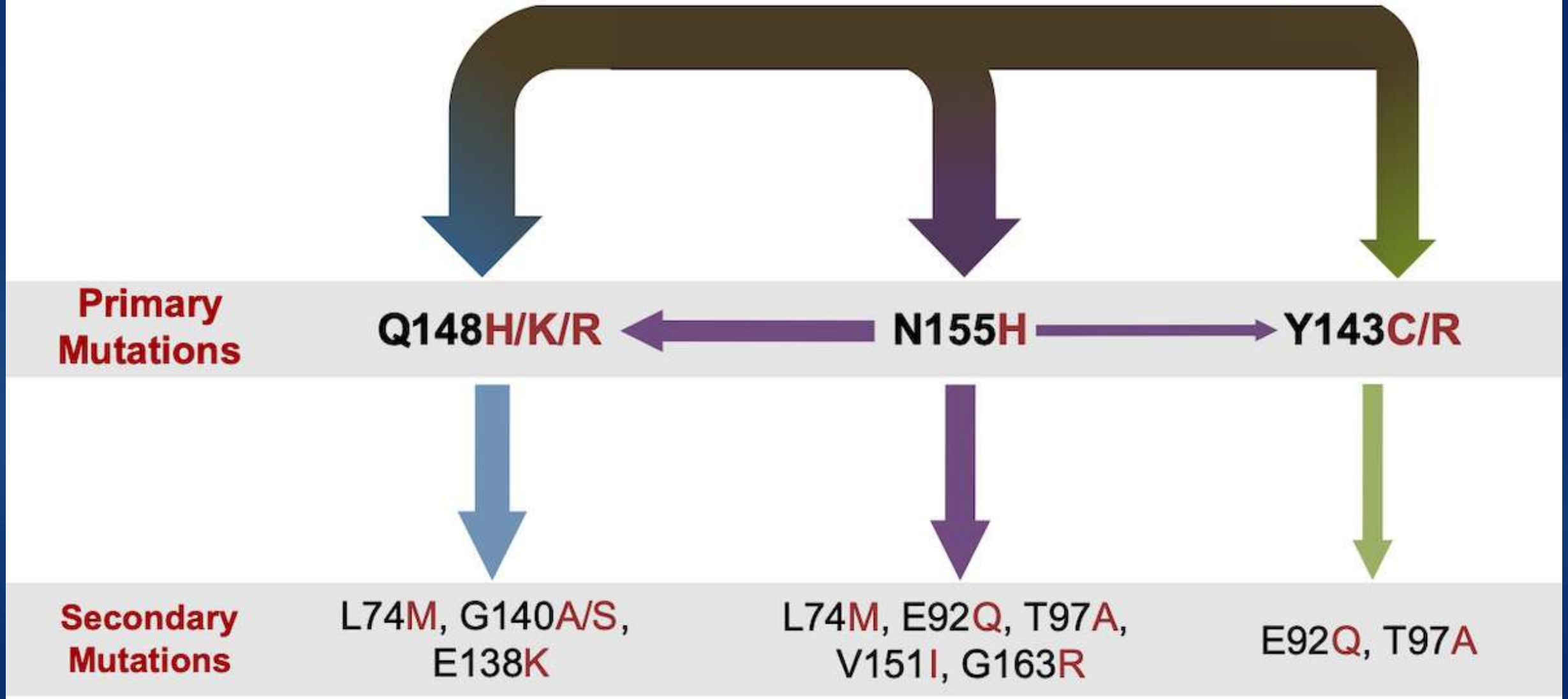
T	E	E	G	Y	S	Q	N
66	92	138	140	143	147	148	155
A I K	Q	K A T	S A C	R C H	G	H R K	H

HIV Integrase



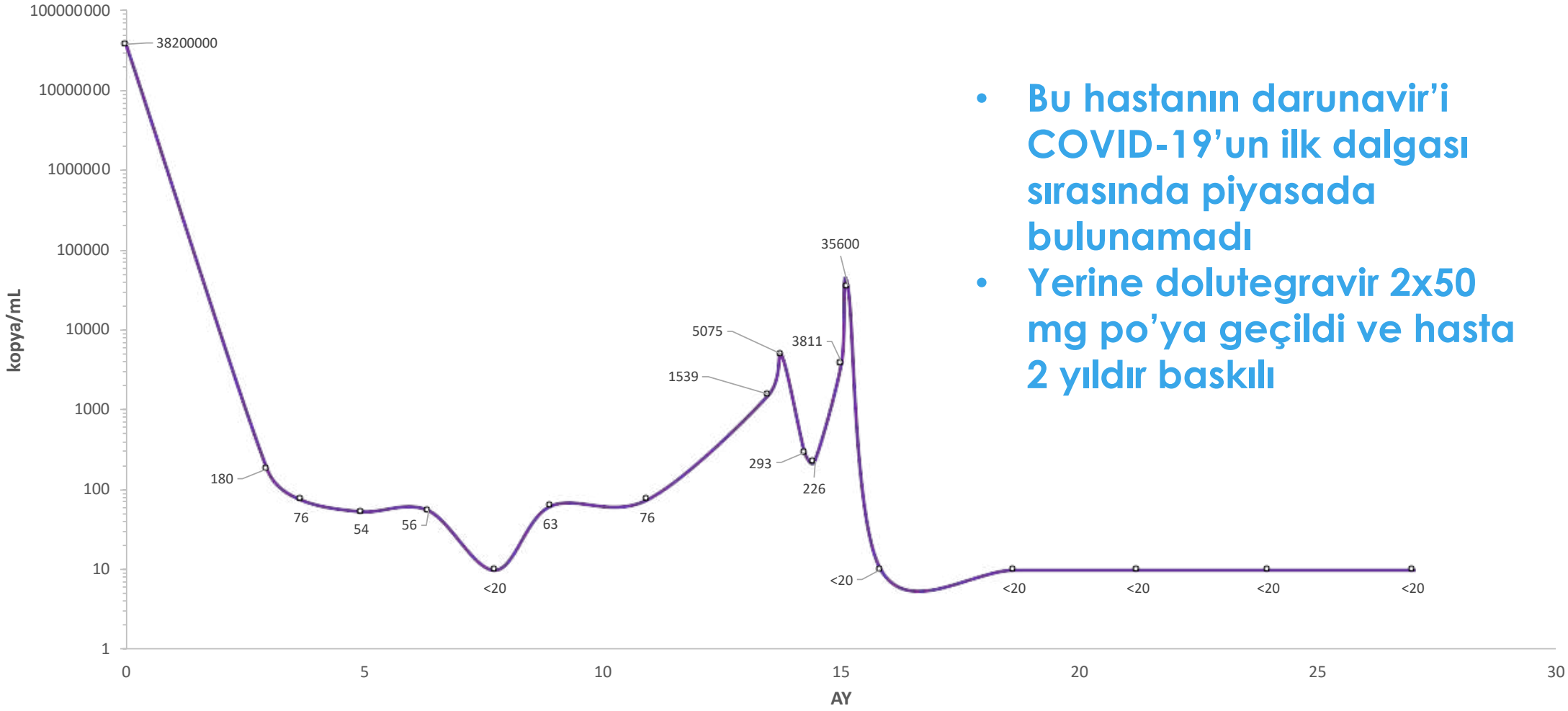
Raltegravir Resistance Pathways

National HIV Curriculum

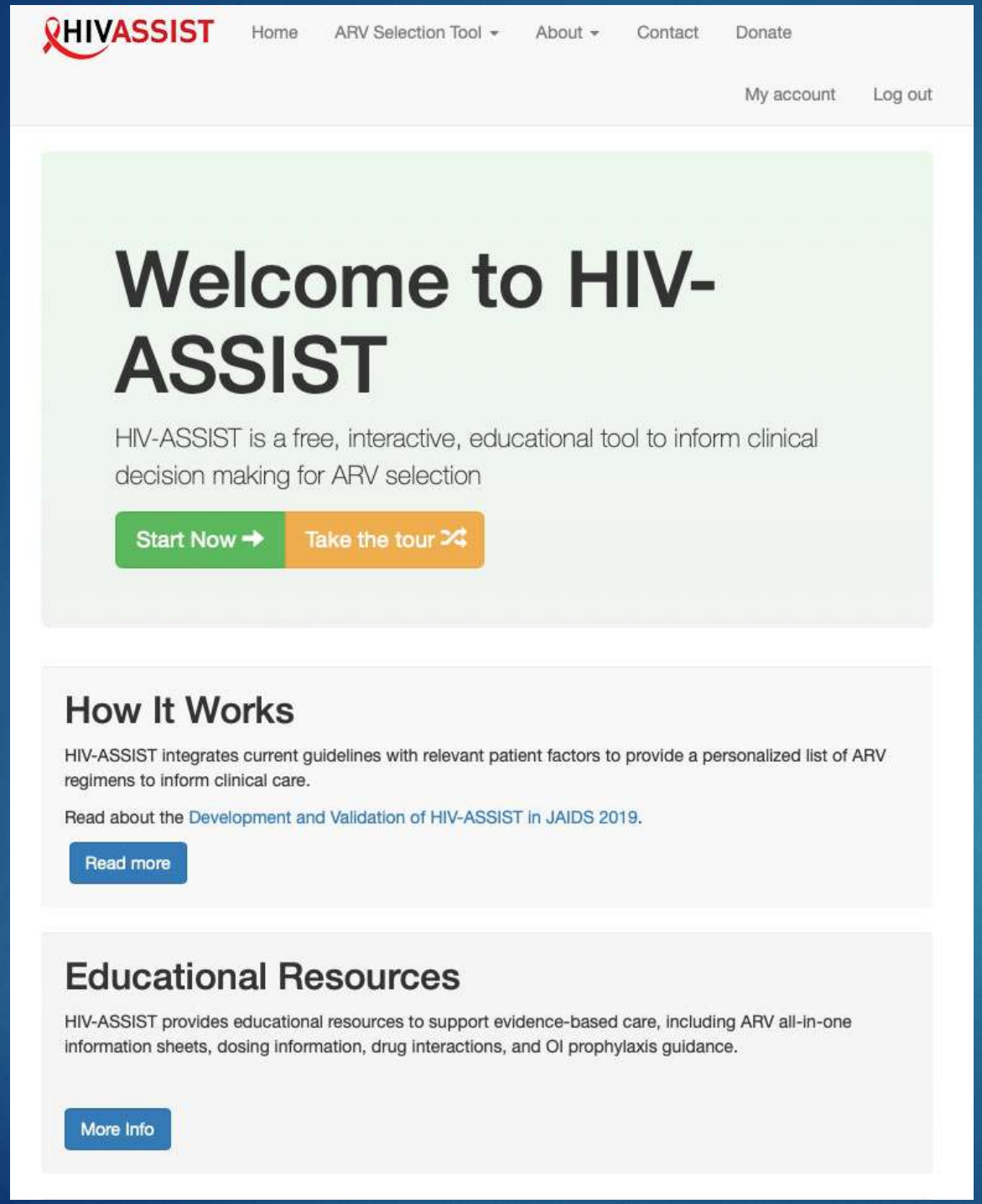


Olgu (raltegravir)

TDF/FTC + LPV/r | TDF/FTC + RAL (2x400 mg) + HREZ | TDF/FTC + RAL | TDF/FTC + DRV + r



- **Bu hastanın darunavir'i COVID-19'un ilk dalgası sırasında piyasada bulunamadı**
- **Yerine dolutegravir 2x50 mg po'ya geçildi ve hasta 2 yıldır baskılı**



SUPPORTING ORGANIZATIONS

CLINICAL CARE OPTIONS®

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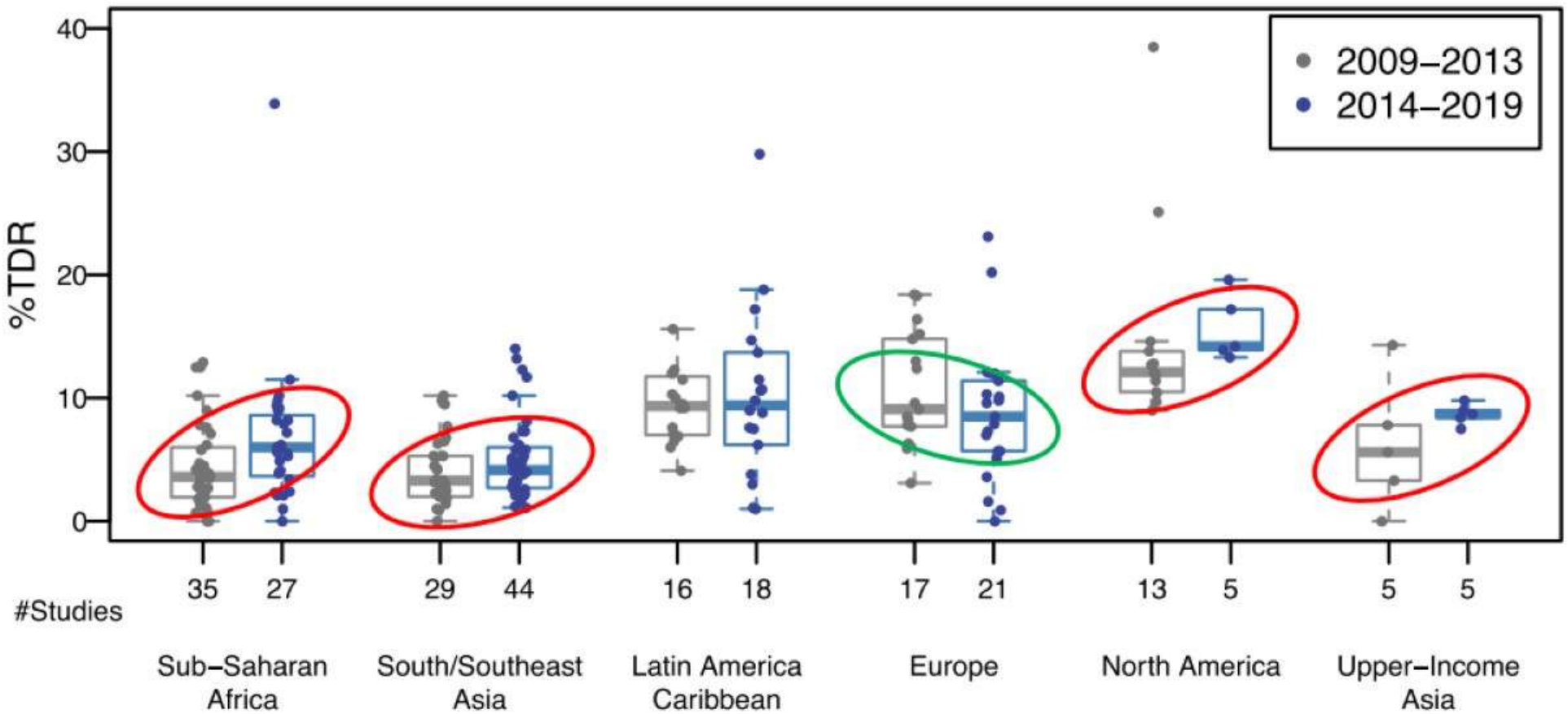
Trends in transmitted drug resistance



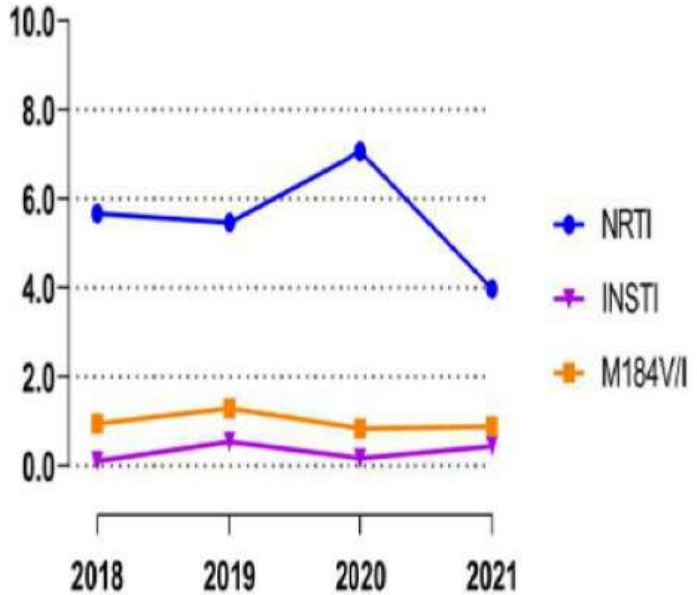
- 125 studies published 2014-2019 (**32,866 persons**) and 122 studies published 2009-2013 (**41,724 persons**) each reporting ≥50 ART-naïve adults
- Two thirds of data from low/middle income countries
- HIV sequences submitted to GenBank

Rhee, JIAS 2020

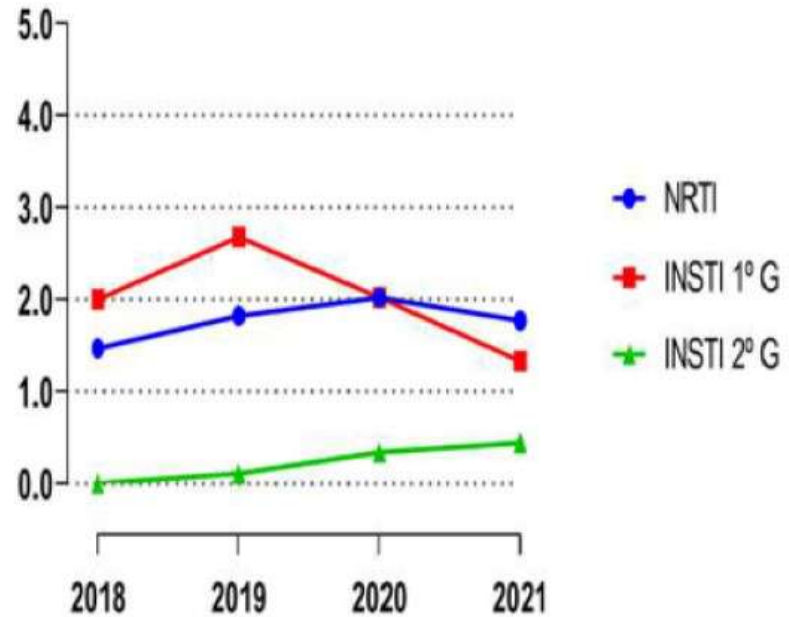
Transmitted drug resistance to integrase-based first-line treatment in Europe

- 2705 ART naïve PLWH from **MeditRes** HIV (France, Greece, Italy, Portugal and Spain) diagnosed in **2018-2021**
- 72% men, median age 37 (30-48) and median viral load 108k (25k-420k)
- **43.7% non-B subtypes** **The prevalence of INSTI-SDRMs was 0.30% and of NRTI-SDRMs was 5.77%**

Prevalence of INSTI and NRTI Surveillance Drug Resistance Mutations across the 4-year study period



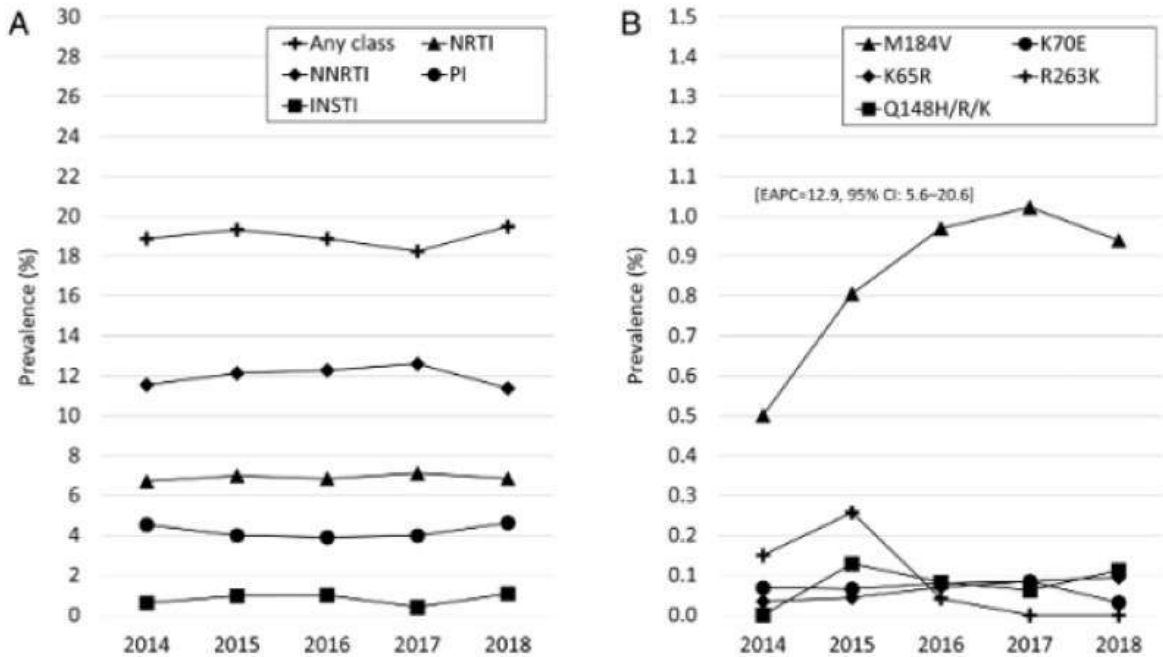
Prevalence of INSTI and NRTI Clinically Relevant Resistance across the 4-year study period



De Salazar, et al CROI 2022 & CID 2022

Transmitted drug resistance in USA

- Drug resistance test performed ≤3 months after HIV diagnosis and reported to the National HIV Surveillance System
- Of 50 747 persons in the analysis, 9616 (18.9%) had ≥1 TDRM.
- **TDRM prevalence was 0.8% for integrase strand transfer inhibitors (INSTIs), 4.2% for protease inhibitors, 6.9% for nucleoside reverse transcriptase inhibitors (NRTIs), and 12.0% for non-NRTIs (K103N the most prevalent, 8.6%).**



TDRM prevalence did not increase or decrease significantly during 2014-2018 overall, for individual drug classes, or for key individual mutations except for M184V (12.9% increase per year; 95% confidence interval, 5.6-20.6%).

➢ **Continued population-level monitoring of INSTI and NRTI mutations, especially M184V and K65R, is warranted amidst expanding use of second-generation INSTIs and PrEP.**

Figure 2. Transmitted drug-resistance–associated mutation prevalence by year for (*A*) individual drug classes and (*B*) key NRTI and INSTI mutations: 28 US states, 2014–2018. Key mutations include those with frequency N >10 in the analysis, and which substantially decrease susceptibility to first-line NRTIs (M184V, K65R, K70E) or INSTIs (Q148H/R/K, R263K). Abbreviations: CI, confidence interval; EAPC, estimated annual percent change; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

McClung RP, et al CID 2022

> Curr HIV Res. 2022 Mar 3. doi: 10.2174/1570162X20666220303104509. Online ahead of print.

Integrase Strand Transfer Inhibitor (INSTI) Genotypic Resistance Analysis in Treatment-nNaive, INSTI Free Antiretroviral-Experienced and INSTI-Experienced Turkish Patients Infected with HIV-1

Murat Sayan [1], Figen Sarigul Yildirim [2], Sila Akhan [3], Ilkay Karaoglan [4], Halis Akalin [5]

- 2018 – 2020
- 50 ART-naif, 69 INSTI hariç ART deneyimli, 82 INSTI deneyimli hasta
- ART-naiflerde: INSTI direnci saptanmamış
- Virolojik başarısızlıkta INSTI mutasyonları
  - raltegravir: E138K, Y143R, S147G, Q148R, N155H ve E157Q
  - elvitegravir: RAL mutations + E92Q, E138K, G140A, S147G ve Q148R
  - dolutegravir: RAL mutations + E192Q, E138K/T, G140A/S, S147G, Q148H/R, N155H, E157Q

FOUR-YEAR ANALYSIS OF GENETIC DIVERSITY AND HIV DRUG RESISTANCE MUTATIONS AMONG HIV-1 TREATMENT-NAIVE TURKISH COHORT

R. Can Sarinoglu [2, 5], U. Sili [4], U. Hasdemir [5], B. Ergan [5], R. Mammadova [4], B. Aksu [5], G. Celik [2], T. Avsar [1], S. Karaketir [3], V. Korten [4]

[1]Bahcesehir University, Faculty of Medicine, Department of Medical Biology
[2]Bahcesehir University, Faculty of Medicine, Department of Medical Microbiology
[3]Istanbul University, Faculty of Medicine, Department of Public Health
[4]Marmara University, Faculty of Medicine, Department of Infectious Disease and Clinical Microbiology
[5]Marmara University, Faculty of Medicine, Department of Medical Microbiology

Table 1. HIV-1 subtype distribution (n=275)

HIV-1 subtype	n (%)
B	164 (59,64)
A	42 (15,27)
F	4 (1,46)
C	3 (1,09)
CRF56_cpx	6 (2,18)
CRF02_AG	5 (1,82)
CRF12_BF	1 (0,36)
CRF28_BF	1 (0,36)
CRF43_02G	1 (0,36)
Rec B, CRF02_AG	42 (15,27)
Rec A, CRF02_AG	1 (0,36)
Rec G, CRF02_AG	3 (1,09)
Rec G, J	2 (0,73)

CRF: Circulating recombinant form, Rec: Recombinant

Table 2. The rates of pre-treatment and transmitted drug resistance mutations in naïve patients (n = 275)

	Pre-treatment drug resistance mutations n (%)	Transmitted drug resistance mutations n (%)
NRTI	24 (8,73)	11 (4)
NNRTI	44 (16)	9 (3,27)
PI	0 (0)	0 (0)
Any	61 (22,18)	20 (7,27)

NNRTI; non-nucleoside reverse transcriptase inhibitors, NRTI; nucleos(t)ide reverse transcriptase inhibitors, PI; protease inhibitors

Table 3. Drug Resistance Mutations (n=275)

Mutations		n	(%)
NRTI	S68G	4	1,46
	A62V	9	3,27
	M41L[a]	4	2,90
	T215D[b], S[c], L, TA	5	1,82
	E44D	1	0,36
	69Del	1	0,36
NNRTI	E138A, EA, G,	31	11,27
	K103N[d], KQ	8	2,9
	K101E[e]	1	0,36
	V179D, E, VE	7	2,55
	V106I	1	0,36
	Y188L[f]	1	0,36

a, b, c, d,e, f: ***Transmitted drug resistance mutations***

Themed Discussion-11

Wednesday, March 6, 2024

Resistance to Second-Generation InSTIs in Mexican PLWH: Emergence of the R263K Mutant

Mexico
2019: EFV/TDF/FTC → BIC/TAF/FTC
2019 – 2024: 215,000 on BIC/TAF/FTC

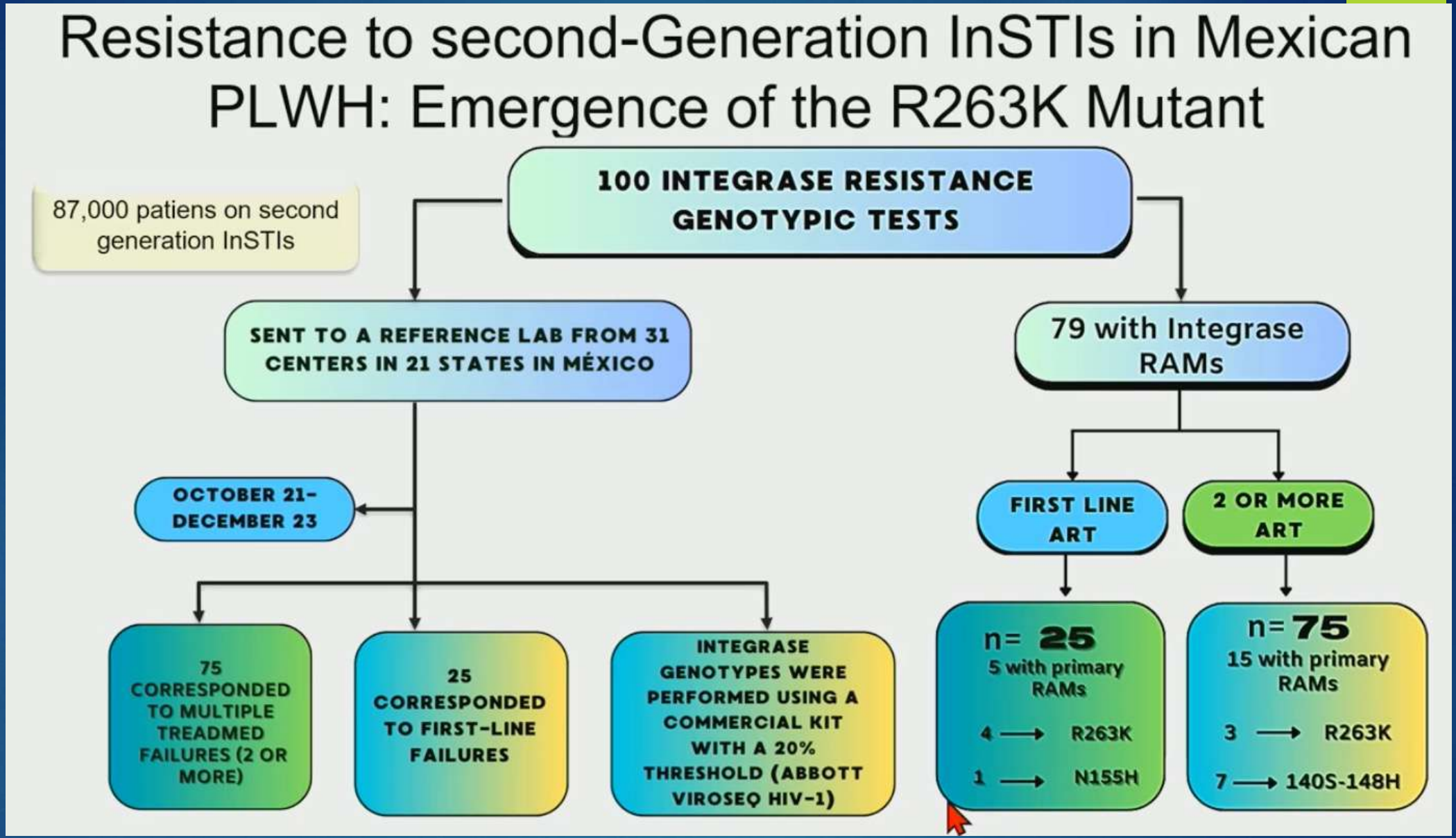
Luis Enrique Soto Ramírez

Instituto Nacional de Ciencias Medicas y Nutricion
Salvador Zubiran
Ciudad de Mexico, Mexico

Disclosure: Dr Soto Ramírez reported no relevant financial relationships with ineligible companies.

CROI 2024

Resistance to second-Generation InSTIs in Mexican PLWH: Emergence of the R263K Mutant



Referral lab

only 100 referrals in 2 years (referral bias?)

5/25 (20%) 15/75 (20%)

Integrase resistance tests with presence of R263K mutation

N	Mutations	Current Scheme	Failure time (Months)	CV at failure	CD4 at failure	Previous treatment
1	**R263K**+V201I+R20K+V21I+T122I	DTG+TDF/FTC	3	298665	22	TDF/FTC+EFV
2	**R263K**+L101I+V201I+V31I+I135V +A49G	DTG+TDF/FTC	21	36320	313	None
3	**R263K**+G118R+E138K+K165N+ D256E+I72L+**M50I**+D253E+S230G +I60M	DTG+TDF/FTC	16	1892	178	None
4	**R263K+M50I**	BIC/TAF/FTC	26	439	45	TDF/FTC+ATV/r
5	**R263K+M50I**+E157Q	BIC/TAF/FTC	14	2753	58	TDF/FTC+EFV
6	**R263K+M50I**	BIC/TAF/FTC	13	2153	206	None
7	**R263K+M50I**	BIC/TAF/FTC	11	4013	137	None

Frequency of R263K mutant:

- 2019-21: 0.3% (2/666)*
- 2021-22: 5%(3/60)
- 2023: 10% (4/40)

When R263K mutation was associated with M50I, viral loads were less than 4000 copies/ml despite long time in virological failure.

* Abstract B11, **IAS - International AIDS Society Conference 2023, Brisbane , Australia.**

naive to INSTIs, low viral load at the time of failure (fitness effect?)
increasing frequency of R263K within years

Integrase resistance tests with combination of G140S plus Q148H.

N	Associated RAMs	Current ART	Failure time (Months)	CV at failure	CD4 at failure	Previous treatment(s)
1	E138A	DRV/c+TDF+DTG	10	51683	353	DRV/r+TDF+**RAL**
2	E138A	FTC+TDF+DTG+DRV/r	22	24846	67	FTC+TDF+EFV
3	E138K	BIC/TAF/FTC	19	264	218	TDF/FTC+EFV
4	L74M+T97A+Y143H	DTG+3TC+ZDV+TDF	17	16541	268	ABC/3TC+TDF+**RAL** ABC/3TC+ZDV+TDF
5	T97A+E138T+Y143R	BIC/TAF/FTC	2	4776	33	3TC+D4T+LPV/r DDI+3TC+LPV/r 3TC+AZT+NVP TDF/FTC+TPV/r ABC+DDI+ATV/r DRV/r+ETV+DTG+TDF/FTC DRV/r+ETV+DTG DRV/r+ETV+**RAL**+T20
6	None	DTG+ABC/3TC	16	4576	671	BIC/TAF/FTC DRV/r+**RAL**
7	None	ETV+DRV/r+DTG	7	266964	460	FTC/TDF+LPV/r

received RAL before, 5/7 failing to DTG, 2/7 failing to BIC

Non–INSTI RAMs In People Failing To 2nd Line Integrase Inhibitors

ART/ Line	Associated INSTIs	NRTI	NNRTI	PI
DTG+TDF/FTC- 2[a]	R20K+V21I+T122I+V201I+**R263K**	A62Y, T215I	K101E,K103N, V106I	None
BIC/TAF/FTC-1[a]	**M50I+R263K**	T215I	None	None
DRV/c+TDF+DTG-2[a]	E138A+**G140S+Q148H**	None	K103N	None
FTC+TDF+RAL+DRV/r -2[a]	E138A+**G140S+Q148H**	T215I	K103N	None
BIC/TAF/FTC-2[a]	E138K+**G140S+Q148H**	T215I	K103N	None
DTG+3TC+ZDV+TDF-2[a]	L74M+T97A+**G140S+**Y143H+ **Q148H**	I15F, E138K, T215IY, K219E	None	L10I
BIC/TAF/FTC-2[a]	T97A+E138T+**G140S+**Y143R+ **Q148H**	L74V, V75I, T215D	L100I,K103N, V106I	V32I, 154L, R57K, A71V, V82T ,L90M
ETV+DRV/r+DTG-2[a]	**G140S+Q148H**	L74I, E138K	K101E, V179L	L10I, I54L, R57K, A71V
TDF/FTC+DTG-1[a]	N155H	T215I	None	None
TDF/FTC+DTG-2[a]	E138A+G140C+Q148R	M41L, T215IS	K101E, V108I	None
ABC/3TC/DTG-2[a]	L74M+E138K+G140A+S147G +Q148R	L74V, T215I	None	I13V, R41K,R57K, 162V, A71V

- Most frequent NRTI mutation was a revertant in 215 position.
- NO M184V WAS FOUND
- NNRTI mutations were associated to previous EFV use.
- Primary PI RAMs were rare.

184V absent !?, revertants at 215th, 103N as NNRTI mutations

Stanford University

HIV DRUG RESISTANCE DATABASE

A curated public database to represent, store and analyze HIV drug resistance data.

Rule	BIC	CAB	DTG	EVG	RAL
R263K	30	60	30	30	15

Rule	BIC	CAB	DTG	EVG	RAL
G140S	10	15	10	30	30
G140S + Q148H	10	0	10	0	0
Q148H	25	60	25	60	60
Total	45	75	45	90	90

Rule	BIC	CAB	DTG	EVG	RAL
E138A	10	15	10	15	15
E138A + G140S	10	15	10	15	15
E138A + Q148H	10	0	10	0	0
G140S	10	15	10	30	30
G140S + Q148H	10	0	10	0	0
Q148H	25	60	25	60	60
Total	75	105	75	120	120

Susceptible: Total score 0 to 9

Potential low-level resistance: Total score 10 to 14

Low-level resistance: Total score 15 to 29

Intermediate resistance: Total score 30 to 59

High-level resistance: Total score >= 60

World Health Organization

HIV drug resistance

Brief report 2024

HIV ilaç direnci DSÖ_2024

- DSÖ, ulusal olarak önerilen birinci basamak ART rejimleri ve PrEP ve maruziyet sonrası profilaksi için kullanılan rejimlerin seçimini bilgilendirmek için birinci basamak ART'ye başlayan veya yeniden başlayan yetişkinler arasında **HIV ilaç direncinin gözetimini** (surveillance) önermektedir
- Daha önce INSTI'ye maruz kalmamış ve DTG içeren ART rejimleri alan ve viral yükü baskılamada başarısız olan bireylerde ortaya çıkan INSTI ile ilişkili ilaç direnci mutasyonlarının yaygınlığı (prevalence) **%3'ün altındaydı**
- ABD Başkanı'nın AIDS'e Karşı Acil Durum Planı'nın desteklediği bazı düşük ve orta gelirli ülkelerdeki son çalışmalar, DTG bazlı ART alan ve tespit edilebilir viremisi olan bireyler arasında **DTG direncinin yaygınlık tahminlerini %3,9 ile %19,6 arasında** bildirmektedir
- Daha fazla ülke DTG tabanlı birinci basamak ART'ye geçerken, DSÖ yalnızca HIV-1'in ters transkriptaz ve proteaz bölgelerinin değil, aynı zamanda **integraz bölgesinin** de genotiplenmesini öneriyor

ÖZET

- HIV ilaç direnci hem ART başarısızlığı sonucu ortaya çıkabilir, hem de ART başarısızlığına neden olabilir
  - ART alırken viral replikasyon ana neden
  - Uyum, uyum, uyum
- Tanı anında, tedavi öncesi ve virolojik başarısızlıkta direnç testi istenmeli
  - RT, polimeraz ve integraz
- ART oluştururken ilaçların aktivitesi göz önüne alınmalı

I. VİRAL İNFEKSİYONLAR VE BAĞIŞIKLAMA SİMPOZYUMU

KLİMİK

HIV Güncelleme, 2. Oturum

HIV ve Direnç

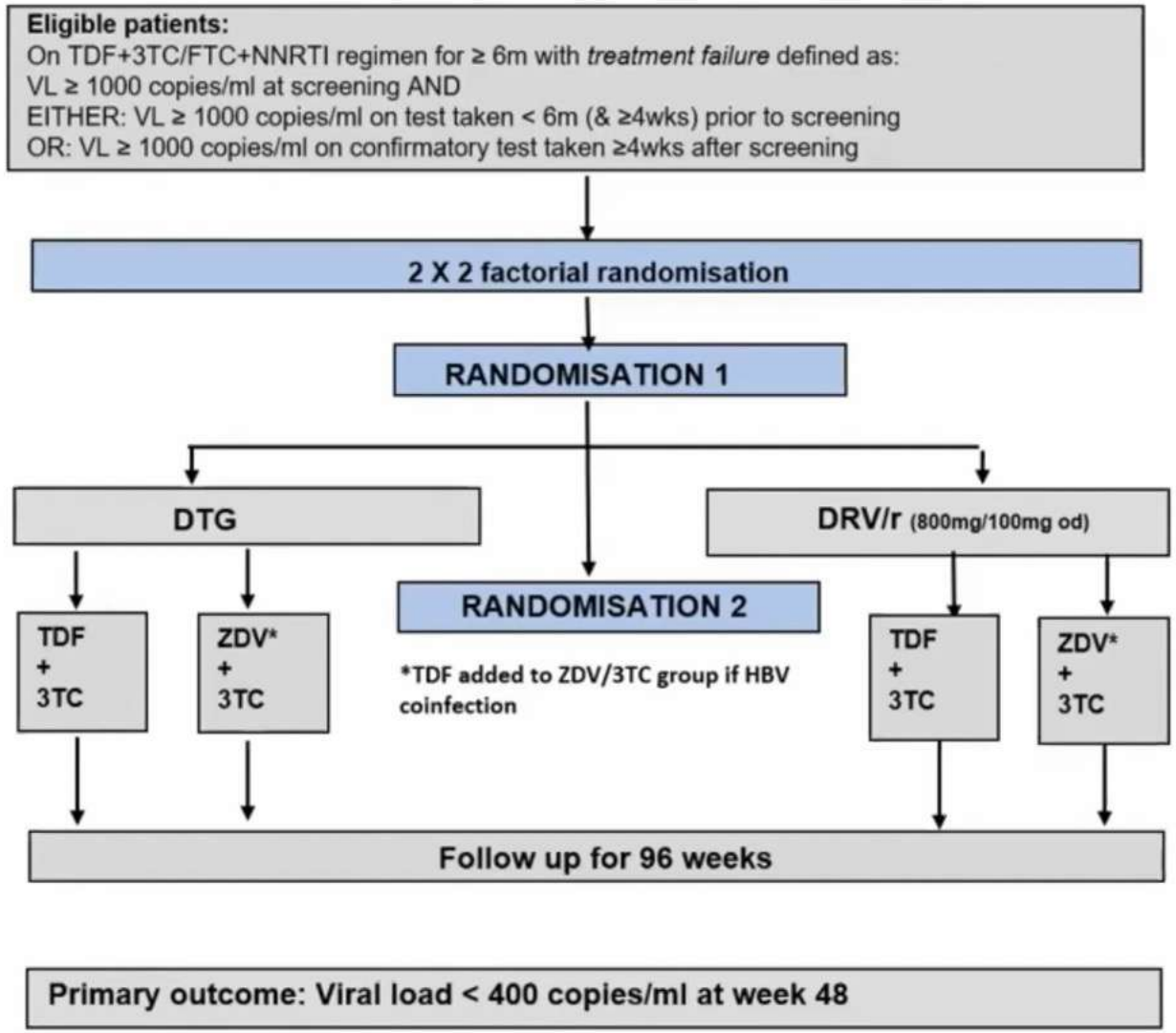
İlginiz için teşekkürler!

Prof. Dr. Uluhan Sili
Marmara Üniversitesi Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD
uluhan@hotmail.com

MARMARA ÜNİVERSİTESİ 1883 | Tıp Fakültesi

21 EYLÜL 2024

DTG vs DRV and TDF vs AZT for 2nd-Line Therapy (NADIA Trial)



n=464 participants

Retrospective GRT

M184V - 87%; K65R - 50%

DTG vs. DRV

<400: DTG (88%), DRV (90%)

<50: DTG (81%), DRV (80%)

TDF vs. AZT

<400: TDF (88%), AZT (85%)

<50: TDF (81%), AZT (80%)

4 patients on DTG developed INSTI DRMs at W48

9 patients on DTG developed INSTI DRMs at W96

Paton N. Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV. *NEJM 2021*

Paton N. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results. Lancet HIV 2022

Drug resistance interpretation: RT

HIVDB 9.6 (2024-03-09)

NRTI Mutations: **K65R** · **M184V**
NNRTI Mutations: None
RT Other Mutations: None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Intermediate Resistance

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Susceptible
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

RT comments

NRTI

- **K65R** confers intermediate reductions in susceptibility to TDF, ABC, and 3TC/FTC. Other than M184VI, it is the most common DRM emerging in patients receiving TDF/XTC. **K65R** increases AZT susceptibility. In NRTI-experienced, INSTI-naive patients with **K65R**, TDF/3TC/DTG is usually highly effective and more effective than AZT/3TC/DTG. However, in patients receiving TDF/3TC/DTG, there is a risk of emergent DTG resistance that does not arise in NRTI-naive patients receiving TDF/3TC/DTG.
- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low/intermediate resistance to ABC (3-fold reduced susceptibility). **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT and TDF and are associated with clinically significant reductions in HIV-1 replication.

Mutation scoring: RT

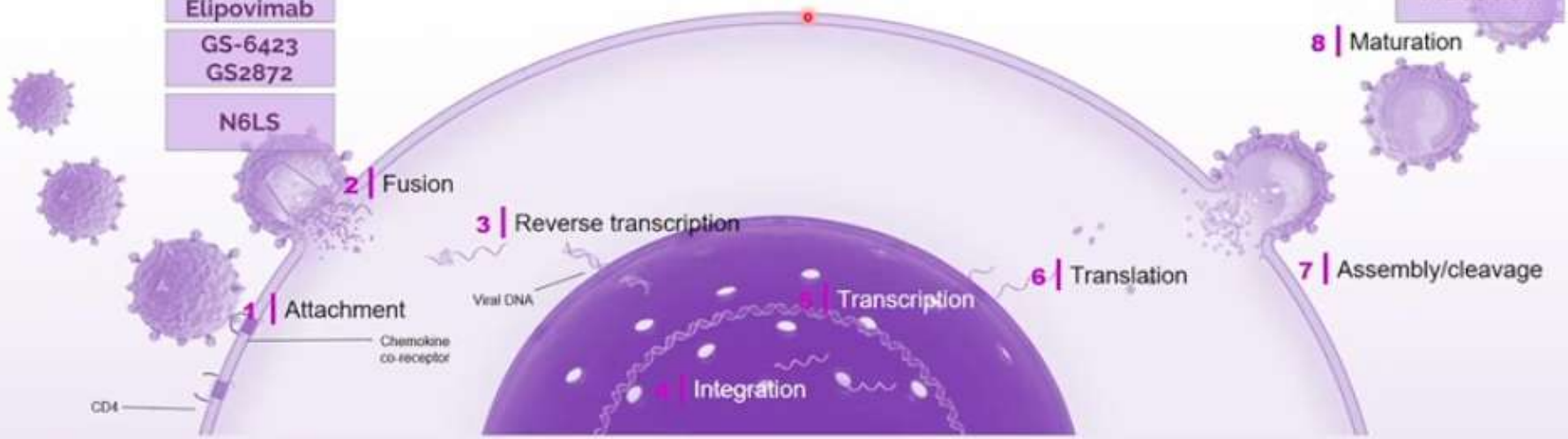
HIVDB 9.6 (2024-03-09)

Drug resistance mutation scores of NRTI: Copy to clipboard

Rule	ABC	AZT	FTC	3TC	TDF
K65R	45	-10	15	15	45
M184V	15	-10	60	60	-10
Total	60	-20	75	75	35

Compounds in clinical development for treatment and prevention

Entry inhibitor	bNAb	NRTI NRTTI	NNRTI	Integrase inhibitor	Protease inhibitor	Capsid inhibitor	Maturation inhibitor	Topical IVR /MPT
Albuvirtide	UB-421	Islatravir	Elsulfavirine	Bictegravir	GS-1156	Lenacapavir	GSK254	Dapivirine
	Leronlimab (PRO-140)	TAF implant	ACC007	S-365598			GSK937	MIV 150 PC1005 gel
	VRC 01/LS VRC 07/LS							EVO-100 gel
	PG121 + Elipovimab							MB66 film
	GS-6423 GS2872							
	N6LS							



HIV LIFE CYCLE

CROI2022
Conference on Retroviruses and Opportunistic Infections

Speaker Info

WEDNESDAY PLENARY SESSION

NEW ANTIRETROVIRALS AND THE FUTURE OF HIV TREATMENT AND PREVENTION

Chloe L Orkin
Queen Mary University of London, London, United Kingdom

J Antimicrob Chemother
doi:10.1093/jac/dkz417

Journal of Antimicrobial Chemotherapy

Integrase strand transfer inhibitor (INSTI)-resistance mutations for the surveillance of transmitted HIV-1 drug resistance

Philip L. Tzou [1]*, Soo-Yon Rhee[1], Diane Descamps[2], Dana S. Clutter[3], Bradley Hare[4], Orna Mor[5], Maxime Grude[6], Neil Parkin[7], Michael R. Jordan[8], Silvia Bertagnolio[9], Jonathan M. Schapiro[10], P. Richard Harrigan[11], Anna Maria Geretti[12], Anne-Geneviève Marcelin[6] and Robert W. Shafer[1] on behalf of the WHO HIVResNet Working Groups

6 September 2019

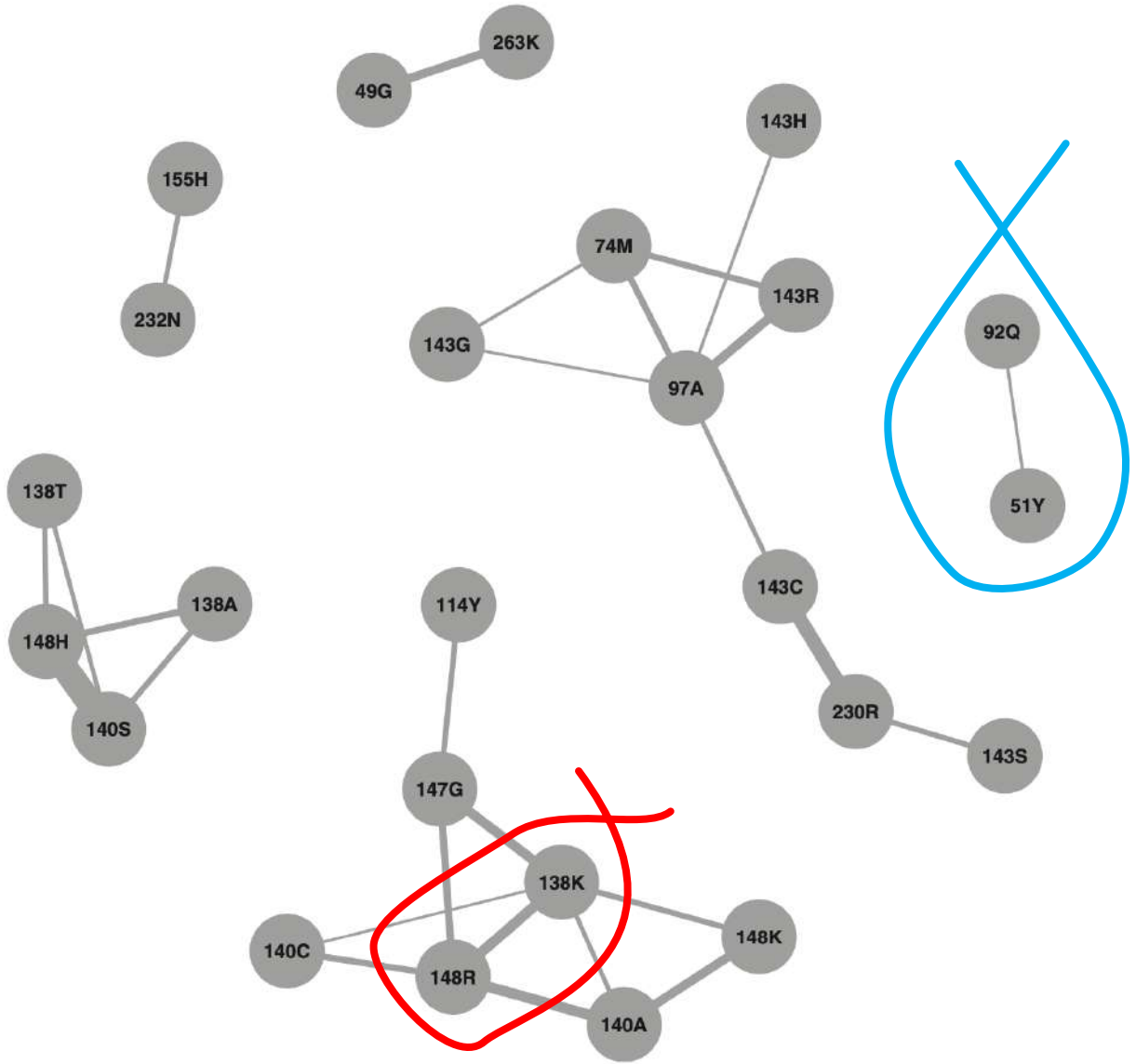
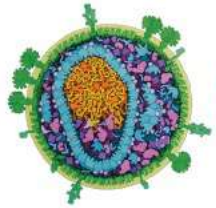


Figure 2. Correlation network analysis of the 25 INSTI-resistance mutations that most frequently co-occurred with one or more other INSTI-resistance mutations. INSTI-resistance mutations having a non-parametric Spearman correlation coefficient (ρ) of >0.075 and a P value ≤0.00001 are linked with an edge. Edge thickness is proportional to ρ, with the greatest thicknesses for the edge between G140S and Q148H (ρ=0.93), Y143C and S230R (ρ=0.65) and G140A and Q148R (ρ=0.38).



CROI
Conference on Retroviruses and Opportunistic Infections

Showing session: RESET

Dolutegravir Resistance in Resource-Limited Settings

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Themed Discussion: Dolutegravir Resistance in Resource-Limited Settings

Session Overview - Dolutegravir Resistance in Resource-Limited Settings
Gert U. van Zyl
Stellenbosch University, Cape Town, South Africa

▶ slides video ⬇ mp3

from CROI 2024 on March 6, 2024 1:30 PM-2:30 PM

Themed Discussion: Dolutegravir Resistance in Resource-Limited Settings

Viremia and Drug Resistance 2 Years After Routine Switching to Dolutegravir-Based First-Line ART (ABSTRACT 676)
Richard J. Lessells
KwaZulu-Natal Research Innovation and Sequencing Platform, KRISP

▶ slides video ⬇ mp3

from CROI 2024 on March 6, 2024 1:30 PM-2:30 PM

Themed Discussion: Dolutegravir Resistance in Resource-Limited Settings

DTG Resistance in Patients with Previous ARV Experience and Viremia in Kenya Receiving DTG-Based ART (ABSTRACT 677)
Leonard Kingwara
Ministry of Health, Nairobi, Kenya

▶ slides video ⬇ mp3

from CROI 2024 on March 6, 2024 1:30 PM-2:30 PM

Themed Discussion: Dolutegravir Resistance in Resource-Limited Settings

Emerging Dolutegravir Resistance in Lesotho (ABSTRACT 678)
Niklaus D. Labhardt
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